THE BRITISH JOURNAL OF OPHTHALMOLOGY

INCORPORATING

THE ROYAL LONDON OPHTHALMIC HOSPITAL REPORTS, THE OPHTHALMIC REVIEW AND THE OPHTHALMOSCOPE.

CONTENTS

Communications

1. Intravitreal Injections of Penicillin: Study on the Levels of Concentration Reached and Therapeutic Efficacy. By Arnold Sorsby and Joseph Unger ... 637
2. Distribution of Penicillin in the Eye after Injections of 1,000,000 Units by the Subconjunctival Retrobulbar and Intramuscular Routes. By Arnold Sorsby and Joseph Unger ... 664
3. The Control of Experimental Infections of the Anterior Chamber and of the Vitreous by Subconjunctival and Retrobulbar Injections of Crystalline Penicillin in Doses of 1,000,000 Units. By Arnold Sorsby and Joseph Unger ... 673
4. Preliminary Note on the Treatment of Hypopyon Ulcer by Crystalline Penicillin in Adrenalin in Doses in Excess of 50,000 Units Injected by Subconjunctival or Retrobulbar Routes. By Arnold Sorsby and Joseph Unger ... 678
5. On Symptoms of the Pulse in the Central Retinal Artery. By W. Rosenzweig ... 681
6. A Case of Pigmented Leiomyoma of the Iris. By Norman Fleming ... 685
7. Observations on Experimental Pneumococcal Infection of the Rabbit's Cornea and on their Treatment with Penicillin. By J. Macalpine and M. Weatherall ... 692
8. Scleral Degeneration—A Case of Scleromalacia Perforans. By S. N. Miles ... 699
9. Technique of Iridectomy. By L. Weekers and R. Weekers ... 704
10. Carbonic Anhydrase and Cataracta Lenta. By A. Bakker ... 710
11. On the Frequency of the Stereoscopic Acuity of Vision. By J. W. Hamilton ... 715
12. A Case of Spontaneous Exophthalmos during Delivery. By [illegible] ... 724

Appointments ... 727

Meetings of Societies ... 727

Notes and Queries ... 727

Correspondence ... 727

Index ... 727

Telephone:
MAYFAIR 8343 (2 lines)

Telegraphic Address:
[illegible], LONDON

JOHN WEISS & SON, LTD.

Surgical Instrument Makers.

287, OXFORD STREET, LONDON, W.1

ESTABLISHED 1787.

GOLD MEDAL AWARDS:
LONDON, 1913. CAIRO, 1926. MADRID, 1933. CAIRO, 1937

ELECTRIC HOT-AIR STERILIZER

THERMOSTATICALLY CONTROLLED

Thermostatic control (Fully Automatic). Range — 200° to 500° F., 93° to 260° C. Heat insulated jacket and heat resistant handles. Low current consumption. Bacteria proof closure. High grade cream stove enamelled and chromium plated finish. Fitted with three removable trays, tray removes, thermometer and bacteria-proof vent.

Inner dimensions — 11" x 5½" x 5½"
Overall dimensions — 16" x 14½" x 10"

PRICE : £38 : 0 : 0

(United Kingdom and Northern Ireland only)

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

DECEMBER, 1948

COMMUNICATIONS

INTRAVITREAL INJECTION OF PENICILLIN: STUDY ON THE LEVELS OF CONCENTRATION REACHED AND THERAPEUTIC EFFICACY

BY

ARNOLD SORSBY *and* JOSEPH UNGAR

LONDON

DIRECT injection of penicillin into the vitreous was considered as a possible method of treatment in the early days of penicillin therapy, when it was held that penicillin injected systemically did not penetrate into the interior of the eye. The early samples of crude penicillin proved, however, highly destructive of the globe when injected intra-vitreally (von Sallmann, Meyer and di Grandi, 1944; Sorsby, 1945; Mann, 1946). In contrast crystalline penicillin is well tolerated (Sorsby and Ungar, 1946), though not altogether devoid of undesirable effects on the retina (Duguid *et al.*, 1947). As adequate therapeutic levels in the vitreous can now be obtained by subconjunctival injection (Sorsby and Ungar, 1946, 1947 and 1948), direct intravitreal injection of penicillin has become largely an academic question. In the following study an attempt is made

TABLE I

Levels (u/ml. or u/gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after intravitreal injection of 5,000 units of pure sodium penicillin into one eye.

Injected Eye.

At	2 hours	4 hours	6 hours	18 hours	24 hours	36 hours	48 hours	64 hours	72 hours
Aqueous ...	> 8	160, >8	>8	> 8, 2, 8	> 8, 1	0·25	0, 0	0, 0	0, 0
Vitreous ...	> 8	>8, >8	>8	> 8, >32, > 32	> 8, 32	4	6, 1	0·06, tr.	0, 0
Anterior tissues	> 8	>15, >8	>8	>10, 80, >285	>12, 100	2·2	tr. tr.	0, 0	0, 0
Posterior tissues	>10	>12, >8	>8	>16, 80, >320	>11, 260	4	0, tr.	0, 0	0, 0
Blood	0	0, 0·06	0·06	0 — —	0 —	—	— —	— —	— —

NOTE—The different values recorded represent estimates in different animals.

to assess the levels and persistence of penicillin injected intravitreally and the efficacy of this procedure in controlling experimental vitreal infection.

1.—Level and persistence of penicillin on direct intravitreal injection

The pure sodium salt of penicillin was used, 5,000 units in 0·05 ml. being introduced by a tuberculin syringe directly into the vitreous, centrally at the equator of the right eye of fully grown rabbits. The animals were killed at 2, 4, 6, 18, 24, 36, 48, 64 and 72 hours, and the penicillin concentration in various ocular tissues determined by the standard capillary method of Fleming. The able (p. 858) shows the results obtained.

Three rabbits received injections of 5,000 units into the vitreous of both eyes. They were killed at 24, 48, and 64 hours respectively. The concentrations reached were not substantially different from those observed where one eye only had been injected.

TABLE II

Levels (u/ml or u/gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after intravitreal injection of 5,000 units of pure sodium penicillin into both eyes simultaneously.

At	24 hours		48 hours		64 hours	
Aqueous	4,	1	tr.	tr.	0,	0
Vitreous	>32,	32	16,	4	0·06,	tr.
Anterior tissues	8,	20	0,	0	0,	0
Posterior tissues	140,	200	0,	1·5	0,	0

NOTE—Each set of two values represents the readings in the right and left eyes of a rabbit.

It would therefore appear that the direct intravitreal injection of 5,000 units pure penicillin gives an adequate intravitreal concentration up to 36 hours—or possibly up to 48 hours. Thereafter there is no penicillin left in the vitreous or other ocular tissues.

The uninjected left eye of those rabbits which received injections in the right only, occasionally showed small values suggestive of some diffusion locally or absorption systemically of the penicillin injected intravitreally.

TABLE III

Levels (u/ml. or u/gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after the intravitreal injection of 5,000 units of pure sodium penicillin in one eye.

Uninjected Eye

At	2 hours	4 hours	6 hours	18 hours	24 hours	36 hours	48 hours	64 hours	72 hours
Aqueous ...	8	0, 0·6	0·5, 0	0, 0·25, 0	0, 0	0, 0	0	0, 0	0, 0
Vitreous ...	8	0, 0	0, 0	0, 0·25, 0	0·06, 0·125	tr. 0	0	0, 0	0, 0
Anterior tissues	0·08	0, 0	0, 0	0, 0·4, 0	0, 0·3	0, 0	0	0, 0	0, 0
Posterior tissues	2	0, 0	0, 0	1·5, 0·4, 0	0, 0·3	0, 0	0	0, 0	0, 0
Blood	—	0, 0·06	0·06, 0	— — 0	0 —	— —	—	— —	— —

NOTE—The different values recorded represent estimates in different animals.

2.—Control of experimental vitreous infection by intravitreal injection of penicillin

Material and technique.—Into the right eye of 12 rabbits each weighing 800-1,000 gms., 1,000,000 organisms of staphylococcus aureus strain 663 were injected in 0·05 ml. of saline. Three animals (Nos. 1-3) were kept as controls; 3 more (Nos. 4-6) had injections of 5,000 units of crystalline penicillin in 0·05 ml. of distilled water 20 hours after infection, whilst treatment was begun 3 hours, and immediately after infection in two further batches of 3 animals (Nos. 7-9 and 10-12 respectively). Both the infecting material and the penicillin were introduced centrally into the vitreous by a tuberculin syringe entered at the equator of the globe. Observations were continued over a period of 60 days.

Results

(1) *Within the first 72 hours.*

Controls (Nos. 1-3). Within 24 hours the vitreous assumed a yellowish reflex visible with the naked eye. The globes were greatly engorged. Twenty-four hours later the corneae were steamy and 24 hours later still panophthalmitis was fully established.

Rabbits treated 20 hours after infection (Nos. 4-6). Heavy vitreous involvement, seen with the naked eye, was present within 24 hours; the globes were grossly engorged. The subsequent course was only slightly less severe than in the control animals.

Rabbits treated 3 hours after infection (Nos. 7-9). No obvious vitreous reflex with the naked eye at 24 hours; some congestion of the globe was present. During the subsequent 2 days the inflammatory reaction became less obvious, though the eyes did not appear normal as congestion persisted.

Rabbits treated at the time of infection (Nos. 10-12). Twenty-four hours later the external appearance of the infected eyes was normal and remained so.

(2) *On the fourth day after infection.*

Controls (Nos. 1-3). All 3 animals showed heavy panophthalmitis. Number 2 was found dead, and the remaining two were destroyed.

Rabbits treated 20 hours after infection (Nos. 4-6). The globes were markedly injected. With the naked eye a greyish-yellow reflex was seen from the vitreous in rabbits Nos. 4 and 5, in No. 6 there was diffuse cloudiness of the cornea, precluding a view of the interior of the eye.

Rabbits treated 3 hours after infection (Nos. 7-9). Ophthalmoscopically the vitreous was organised in No. 8, and turbid with grey organised masses in rabbits Nos. 7 and 9. The globes were somewhat injected.

Rabbits treated at the time of infection (Nos. 10-12). The vitreous was turbid in all three rabbits on ophthalmoscopic examination. A red reflex was present in Nos. 11 and 12, though white opacities were also seen; in No. 10 the vitreous was as cloudy as in the rabbits treated 3 hours after infection.

(3) *On the 11th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4-6). One of these three (No. 5) had died 6 days previously. Of the two survivors, one (No. 6) showed a grossly infected eye with a steamy cornea. The second (No. 4) showed iritis with an organized vitreous.

Rabbits treated 3 hours after infection (Nos. 7-9). No. 7 showed a contracted pupil. There was a good red reflex, and some white vitreous opacities. No. 8 showed posterior synechiae and an organised vitreous. The condition of No. 9 was intermediate between that of No. 7 and No. 8; there was a red reflex, but fundus details were not visible.

Rabbits treated at the time of infection (Nos. 10-12). No. 12 had died 6 days previously. No. 10 showed a red reflex, but massive vitreous opacities, mainly white globules were also present. There were white exudates in the fundus below. The changes present were more severe than those seen in No. 9. In No. 11 there was a good red reflex, the pupil was fairly well dilated, but vitreous opacities and fundus reactions as in No. 10 were present.

(4) *On the 25th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4 and 6). Of the two surviving rabbits No. 4 showed a quiet eye with a partially occluded pupil and organized vitreous. No. 6 was very similar: the vitreous was a completely organised yellow mass.

Rabbits treated 3 hours after infection (Nos. 7-9). The result in No. 7 was excellent. The eye was quiet and the vitreous clear, except for two small residual opacities below. In the other two rabbits, the eyes were quiet; No. 8 showed a fairly massive opacity centrally in the vitreous, whilst in No. 9 there were diffuse vitreous opacities obstructing a view of the fundus.

Rabbits treated at the time of infection (Nos. 10 and 11). Both the surviving rabbits showed quiet eyes. In No. 10 the fundus could be seen readily, though there were still some vitreous

opacities. No. 11 was likewise satisfactory, but showed rather more vitreous opacity, and a localised fundus lesion below.

(5) *On the 46th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4 and 6). In rabbit No. 4 the vitreous was completely organised. The animal was destroyed. In rabbit No. 6 the pupil was bound down, the vitreous organised and the cornea showed extensive infiltrates.

Rabbits treated 3 hours after infection (Nos. 7-9). Two of these rabbits (Nos. 7 and 9) showed little more than fine vitreous opacities. The eyes were regarded as good functioning organs clinically. Rabbit No. 8 on the other hand showed a fairly massive vitreous opacity.

Rabbits treated at the time of infection (Nos. 10 and 11). Rabbit No. 10 showed localised vitreous opacities with an extensive fundus lesion below. There was massive organisation of the vitreous in No. 11.

(6) *On the 60th day after infection.*

There were no substantial differences from the observations on the 46th day, except that Rabbit No. 11—one of those treated immediately after infection—now showed a grey reflex from organised vitreous, readily seen with the naked eye.

Comment

These results are not particularly encouraging. Only two of the three rabbits treated 3 hours after infection and only one, possibly two, of the three treated immediately after infection could be regarded as having good functioning eyes clinically. In the remaining animals the infected eyes were lost. It is clear that penicillin greatly influences the course of the infection, but it is also obvious that one intravitreal injection of 5,000 units is not sufficient to overcome fully a heavy experimental infection, though administered 3 hours after infection, or even at the time of infection. Treatment begun 20 hours after infection can prevent panophthalmitis at the expense of an organised vitreous which destroys the eye functionally. Repeated intravitreal injections begun early in mild infections might give better results, but the intolerance of the vitreous to any injections, and the apparent special liability to retinal damage from penicillin administered intravitreally, are serious limiting factors.

Summary

1. Adequate antibacterial levels persist in the vitreous for 36 hours and possibly 48 hours after direct intravitreal injection of 5,000 units crystalline penicillin in 0·05 ml. of water.

2. In heavy experimental infection of the vitreous (1,000,000 organisms of staphylococcus aureus) 5,000 units crystalline penicillin injected into the vitreous had some slight effect if given 20 hours after infection; panophthalmitis was prevented but the vitreous was organised. When treatment was begun 3 hours, or immediately after infection, 3—possibly 4—out of 6 treated eyes could be regarded as clinically functioning eyes.

REFERENCES

DUGUID, J. P., GINSBERG, M., FRASER, I. C., MACASKILL, J., MICHAELSON, I. C. and ROBSON, J. M. (1947).—*Brit. Jl. Ophthal.*, Vol. XXXI, 193.
MANN, I. (1946).—*Brit. Jl. Ophthal.*, Vol. XXX, p. 134.
SORSBY, A. (1945).—*Brit. Jl. Ophthal.*, Vol. XXIX, p. 511.
SORSBY, A. and UNGAR, J. (1946).—*Brit. Med. Jl.*, ii, p. 723.
——— (1947).—*Brit. Jl. Ophthal.*, Vol. XXXI, p. 517.
——— (1948).—*Ibid.* This issue, p.864.
v. SALLMANN, L., MEYER, K. and DI GRANDI, J. (1944).—*Arch. Ophthal.* (Chicago), Vol. XXXII, p. 179.

DISTRIBUTION OF PENICILLIN IN THE EYE AFTER INJECTIONS OF 1,000,000 UNITS BY THE SUBCONJUNCTIVAL, RETROBULBAR AND INTRAMUSCULAR ROUTES

BY

ARNOLD SORSBY *and* JOSEPH UNGAR

LONDON

IN earlier studies (Sorsby and Ungar, 1946 and 1947) it was shown that adequate therapeutic levels could be obtained intra-ocularly by injection of large doses of penicillin subconjunctivally. Attention was drawn to the fact that it was also possible to obtain adequate intra-ocular concentrations by systemic administration of massive doses. (Struble and Bellows, 1944; Town, Frisbe and Wisda, 1946; Town and Hunt, 1946; and Sorsby and Ungar, 1946.) It was also shown that the levels reached and maintained by subconjunctival injection were higher than those obtained by other routes. Subconjunctival injections gave higher and more persistent levels when the penicillin was dissolved in adrenalin solution 1 :1,000 instead of water. There also emerged the fact that the use of 50,000 units as a subconjunctival dose tended to give not only higher but more persistent intra-ocular levels of concentration than with doses of 20,000 units.

The present study deals with the levels obtained when the dose of penicillin was 1,000,000 units injected subconjunctivally in

the rabbit. These findings (Table I) are compared with those obtained on the injection of the same dose retrobulbarly (Table II) and systemically (Table III). The experimental technique and the methods of estimating penicillin levels employed have been described in the two earlier publications.

1.—Intra-ocular levels of penicillin on the injection of 1,000,000 units crystalline penicillin G. subconjunctivally

Crystalline penicillin G. (Glaxo) was used throughout. It is readily soluble; 1,000,000 units were dissolved in either 1 ml. of distilled water or 1 ml. of adrenalin solution 1 : 1,000. The injection was well tolerated and such conjunctival swelling as appeared had completely subsided within 48 hours. Occasionally a crescentic white infiltrate was seen on the limbus near the site of the injection. This, too, tended to disappear within that time. The following summary table shows the values reached in the aqueous and vitreous at different time intervals with the two different solvents.

SUMMARY TABLE I

Levels (u/ml.) reached in the aqueous and the vitreous on the subconjunctival injection of 1,000,000 units Crystalline penicillin G. dissolved in water or adrenalin solution 1 : 1,000.

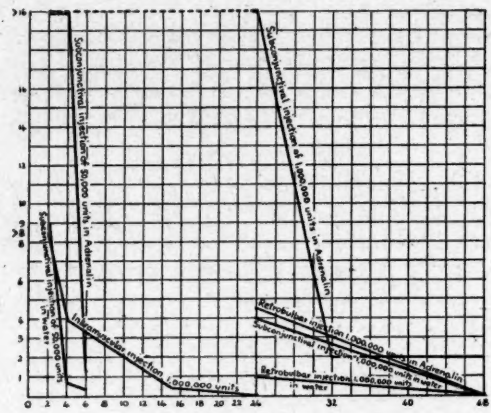
	Time after injection	Injected eye		Uninjected eye	
		Penicillin dissolved in water	Penicillin dissolved in adrenalin	Penicillin dissolved in water	Penicillin dissolved in adrenalin
Aqueous	24 hours	0·25, 8	>16	>2, 4	>4
	32 „	Not determined	>2	Not determined	0·25
	48 „	0	2, >2	0	0·05, 0·03
Vitreous	24 hours	0·125, 8	8	1, 4	0·25
	32 „	Not determined	>2	Not determined	0
	48 „	0	0·25, >2	0·25	0, 0·25

Note :—The different values recorded represent estimates in different animals.

The following conclusions appear warranted :—

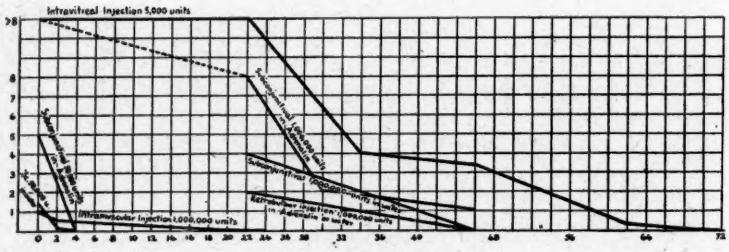
(1) In contrast to the levels reached with relatively low doses of penicillin, adequate concentrations lasting for at least 48 hours can

be achieved in the injected eye with subconjunctival injection of 1,000,000 units in adrenalin solution 1 :1,000. With doses of 50,000 units in adrenalin the aqueous concentrations at six hours was 1·25 U/ml., and 0·03 U/ml. for the vitreous (Sorsby and Ungar, 1947); with a dose of 1,000,000 units the aqueous concentration after 48 hours was of the order of 2 U/ml. and the vitreous concentration between 0·25 and 2 units. The vitreous level on subconjunctival injection of 1,000,000 units in adrenalin is of the same order as that obtained by direct intra-vitreal injection of 5,000 units (Graphs 1 and 2).


Subconjunctival injection of 50,000 units in Adrenalin
Subconjunctival injection of 50,000 units in water
Intravitreal injection 1,000,000 units
Subconjunctival injection of 1,000,000 units in Adrenalin
Retrobulbar injection 1,000,000 units in Adrenalin
Subconjunctival injection of 1,000,000 units in water
Retrobulbar injection 1,000,000 units in water

GRAPH 1.

Levels of penicillin u/ml. in the aqueous.


Intravitreal Injection 5,000 units
Subconjunctival injection 50,000 units in Adrenalin
Subconjunctival injection 50,000 units in water
Intravitreal injection 1,000,000 units
Subconjunctival injection 1,000,000 units in Adrenalin
Subconjunctival injection 1,000,000 units in water
Retrobulbar injection 1,000,000 units in Adrenalin
Retrobulbar injection 1,000,000 units in water

GRAPH 2.

Levels of penicillin in the vitreous.

(2) The value of adrenalin in establishing high levels and maintaining them is apparent from the comparison of the first and second column of summary table I; without adrenalin the levels are both lower and less persistent; at 48 hours neither the aqueous or vitreous contained any penicillin when the agent was injected without adrenalin (Graphs 1 and 2).

(3) Much of the penicillin injected subconjunctivally diffuses in the surrounding tissue. Though the blood showed no penicillin at 32 hours and at 48 hours when adrenalin was used as the solvent for penicillin, considerable levels could be obtained in the uninjected eye. Part of the intra-ocular concentration in the injected eye may be produced by systemic absorption from the subconjunctival depot. This fraction is, however, not significant as can be seen from the intra-ocular levels obtained by the injection of 1,000,000 units penicillin intramuscularly. (Recorded below, section 3.)

2.—Intra-ocular levels of penicillin on the injection of 1,000,000 units crystalline penicillin G. retrobulbarly

When a dose of 1,000,000 units of crystalline penicillin G. is injected deep into the orbit, high intra-ocular levels can be obtained

SUMMARY TABLE II

Levels (u/ml.) reached in the aqueous and the vitreous on the retrobulbar injection of 1,000,000 units Crystalline penicillin G. dissolved in water or adrenalin.

	Time after injection	Injected eye		Uninjected eye	
		Penicillin dissolved in water	Penicillin dissolved in adrenalin	Penicillin dissolved in water	Penicillin dissolved in adrenalin
Aqueous	24 hours	1, 1	1, 8	1, 1	1, 0·5
	48 „	0·25, 0·125	0·06, 0·06	0·25, 0·06	0·125, 0
Vitreous	24 hours	2, 2	2, 2	0·5, 0·5	0·5, 0·5
	48 „	0·125, 0·03	0·03, 0·125	0·03, 0·25	0·06, 0·03

Note :—The different values recorded represent estimates in different animals,

in both the aqueous and vitreous at 24 hours, and effective antibacterial levels are still present at 48 hours. As can be seen from the summary table II there is no tangible difference in the levels reached in the injected and the uninjected eyes (suggesting ready diffusion throughout the surrounding tissues). When penicillin is injected in adrenalin solution the levels obtained with retrobulbar injection, though considerable, are distinctly lower than those obtained by subconjunctival injection.

The levels obtained with retrobulbar injection of adrenalin solution of penicillin, though lower than those obtained from subconjunctival injection, are, however, distinctly higher than those obtained from intramuscular injection (Graphs 1 and 2).

3.—Intra-ocular levels of penicillin on the injection of 1,000,000 units amorphous yellow penicillin intramuscularly

Summary table III shows the levels reached in the aqueous and vitreous on the injection of an adrenalin solution of 1,000,000 units amorphous penicillin intramuscularly.

SUMMARY TABLE III

Levels (u/ml.) reached in the aqueous and the vitreous on intramuscular injection of 1,000,000 units penicillin dissolved in water.

Time after injection	Aqueous	Vitreous
1 hour	>8, >8	>8, 4
2 hours	>8, >8	1, 1
3 „	8, 8	2, 1
4 „	4, 4	0·5, 0·25
15 „	>2, >2 ; 0·25, 0	>2·0, 0·25 ; 0, 0
24 „	0, 0 ; 0, 0	0, 0 ; 0, 0

(Each set of two values represents the readings in the right and left eyes of an animal).

It will be seen that after four hours the vitreous level is low and the aqueous level has dropped considerably. At 15 hours there is still a considerable aqueous level and a lesser vitreous level, but at 24 hours, all the levels are nil. It is clear that local administration, whether by the retrobulbar or subconjunctival route, is superior to intramuscular injection (Graphs 1 and 2). As the systemic dose for man to correspond to 1,000,000 units intramuscularly in the rabbit must run into many millions, intramuscular injection has no advantage over local administration and many disadvantages.

In the rabbit doses lower than 1,000,000 units appear to give relatively poor results. This is seen from summary table IV showing concentrations reached with injections of 500,000 units and 250,000 units.

SUMMARY TABLE IV

Levels (u/ml.) of penicillin reached in the aqueous and vitreous on the intramuscular injection of 500,000 units and 250,000 units penicillin dissolved in water.

	Aqueous	Vitreous
500,000 units After 4 hours ...	1, 2	0·06, 0·1
250,000 units After 4 hours ...	0·5, 0·5; 2, 2; 0·25, 0·5; 0·5, 0·5	0·06, <0·06; 0·5, 0·5; 0·03, 0; 0, 0·03
After 5 hours ...	2, 2	0·5, 0·125
After 6 hours ...	1, 0·5; 0·03, 0·03; 0·06, 0·125	Tr., Tr.; 0, 0; Tr., Tr.
After 7½ hours ...	0, 0·03; Tr., Tr.	0, 0; 0, 0

(Each set of two values represents the readings in the right and left eyes of an animal).

TABLE I

Distribution of penicillin in ocular tissues after subconjunctival injection of 1,000,000 units crystalline penicillin G in 1·0 ml. of water or adrenalin solution 1 : 1,000.

	Penicillin levels in units per ml. of fluid or per gm. of tissue						
Solvent	Distilled Water			Adrenalin 1 : 1,000			
Hours after injection	24 hours		48 hours	24 hours	32 hours	48 hours	
INJECTED EYE							
Aqueous	0·25,	8	0	<16·0	>2	>2,	2
Vitreous	0·125,	8	0	8	>2	>2,	0·25
Cornea	1,	30	15	528	22	>36,	42
Lens	10,	<0·3	20	4	>5	>6·5,	<0·1
Anterior sclera ...	>8,	5·5	7·5	—	6	>10,	—
Posterior sclera ...	>8,	14	3·12	—	>10	7·0,	—
Anterior uvea ...	<8,	44	3·0	—	>12	7·0,	—
Posterior uvea ...	<10,	25	<4·5	>300*	>36	50,	6·8*
Extra-ocular muscles	6,	12·5	30	—	>50	>50,	—
BLOOD	0·00	—	—	—	0·00	0·00	—
UNINJECTED EYE							
Aqueous	>2,	4	0	>4	0·25	0·05,	<0·03
Vitreous	1,	4	0·25	0·25	0	0,	0·25
Cornea	5,	1·8	<4·5	40	>12	>16,	0·72
Lens	>2·5,	<0·3	<0·7	4·5	0·6	>3·0,	0·15
Anterior sclera ...	0·38,	5	18	—	>3·2	>8,	—
Posterior sclera ...	1·6,	18	7·5	—	>5·0	>6,	—
Anterior uvea ...	>8,	<0·4	<2·25	—	>10	>10,	—
Posterior uvea ...	5,	2·5	<6	<25*	>20	>16,	0·65*
Extra-ocular muscles	>20,	7·5	3·9	—	>30	>30,	—

* Posterior tissues.

(The different values recorded represent estimates in different animals).

TABLE II

Distribution of penicillin in ocular tissues after retrobulbar injection of 1,000,000 units crystalline penicillin G in 1·0 ml. of water or of adrenalin solution 1 : 1,000.

	Penicillin levels in units per c.c. of fluid or per gm. of tissue							
Solvent	Distilled Water				Adrenalin 1 : 1,000			
Hours after injection	24 hours		48 hours		24 hours		48 hours	
INJECTED EYE								
Aqueous	1,	1	0·25,	0·155	1,	8	0.06,	0.06
Vitreous	2,	2	0·125,	0·03	2,	2	0.3,	0.125
Cornea	> 30,	> 30		—	< 30,	> 30	—	—
Anterior sclera ...	> 20,	> 20		—	> 20.	> 20	—	—
Posterior sclera ...	13,	15		—	7,	14	—	—
Anterior uvea ...	20,	20	5,	2·5	5,	30	40,	2.5
Posterior uvea ...	> 22,	> 22		—	> 20,	> 19	—	—
BLOOD	0·25,	0·25	0,	0·03	0·125.	0·125	0,	0
UNINJECTED EYE								
Aqueous	1,	1	0·25,	0·06	1,	0·5	0.125,	0
Vitreous	0·5,	0·5	0·03,	0·25	0·5,	0·5	0.06,	0.03
Cornea	4,	6	3·5,	5·5	4,	4	2.5,	5.3
Anterior sclera ...	5,	16	3·5,	4·5	16,	9	2.3,	3.5
Posterior sclera ...	6,	6	1·5	2·5	6,	6	2.4,	0.75
Anterior uvea ...	0·75,	3·5	4·5	2·2	3·5,	1·5	2.2,	2.2
Posterior uvea ...	0·65,	1·2	4,	4	4.	0·5	0·75,	3

(The different values recorded represent estimates in different animals).

TABLE III

Distribution of penicillin in ocular tissues after intramuscular injection of doses of 250,000, 500,000 and 1,000,000 units of amorphous yellow penicillin in distilled water.

Dose injected ...	250,000 units				500,000 units	1,000,000 units					
Hours after injection	4 hours	5 hours	6 hours	7½ hours	4 hours	1 hour	2 hours	3 hours	4 hours	15 hours	24 hours
Aqueous	0·5, 0·5;	2, 2;	1, 0·5;	0, 0·3;	1, 2·0	>8·0, >8	>8, >8	8, 8	4, 4	2·0, 2·0;	0. 0.
	2, 2;	—	0·03, 0·03;	Tr. Tr.	—	—	—	—	—	0·25, 0;	0. 0.
	0·25, 0·5;	—	0·06, 0·125	—	—	—	—	—	—	—	—
	0·5, 0·5;	—	—	—	—	—	—	—	—	—	—
Vitreous	0·6, <0·06;	0·5, 0·125;	Tr. Tr.	0, 0;	0·06, 0·1	>8·0, 4	1, 1	2, 1	0·5, 0·25	2·0, 0·25;	0. 0.
	0·5, 0·5;	—	0, 0;	0, 0;	—	—	—	—	—	0, 0;	0. 0.
	0·03, 0;	—	Tr. Tr.	—	—	—	—	—	—	—	—
	0, 0·03;	—	—	—	—	—	—	—	—	—	—
Cornea	0·5, 0·25;	0·18, 0·21;	<0·22, 0·18;	—	0·75, 0·75	>72, 44	8 5, 7	9·5, 8·75	4·5, 4	—	—
	0·25, 0·18;	—	—	—	—	—	—	—	—	—	—
Anterior tissues ...	0·08, 0·07;	0·11, 0·26;	<0·1, 0·1;	<0·045, <0·045;	0·5, 0·2	>30, >32	16, 9	2, 6·5	6·0, 7	0·65, 0·65;	0. 0.
	0·08, 0·09;	—	<0·875, 0·045;	<0·06, <0·04;	—	—	—	—	—	0, 1·25;	0. 0.
	0·08, 0·2;	—	0·06 0·04;	—	—	—	—	—	—	—	—
	1·2, 0·8;	—	—	—	—	—	—	—	—	—	—
Posterior tissues ...	0·12, 0·18;	0·18, 0·16;	0·165, 0·21;	<0·1, <0·07;	0·25, 0·2	>56, >48	20, 24	22, 15	18, 10	0·3, 0·65;	0. 0.
	0·125, 0·165;	—	<0·08, <0·09;	<0·07, <0·06;	—	—	—	—	—	0, 1·15;	0. 0.
	0·046. 0·5;	—	<0·05, <0·05;	—	—	—	—	—	—	—	—
	0·375, 0·625;	—	—	—	—	—	—	—	—	—	—
Lid conjunctiva ...	0·75, 1·0;	0·51, 0·44;	0·2 <0·46;	—	3·2, 1·6	>40, >40	24, 32	40, 40	25, 15	—	—
	0·33, 0·34;	—	—	—	—	—	—	—	—	—	—
Bulbar conjunctiva ...	1·25, 1·2;	0·8, 0·51;	0·3, 0·3;	—	4, 3·75	>136, >60	144, >56	50, 23	23, 20	—	—
	<1·2, <1·5;	—	—	—	—	—	—	—	—	—	—
Blood	2, 0·5	0·5 —	0·5, —	2, 2	4	>64 —	>64 —	>64 —	>16 —	0·13, 0·13	0·25; 0·06
	>4, >4	— —	>4, >4	— —	— —	— —	— —	— —	— —	— —	— —

Each set of two values represents the reading in the right and left eyes of an animal.

Discussion and Summary

The present study confirms and extends the established observation that penicillin penetrates in adequate therapeutic levels into the interior of the eye if sufficiently massive doses are employed systemically. It is also shown that the local administration of penicillin, whether by retrobulbar or subconjunctival route, gives distinctly higher and more maintained intra-ocular levels than an injection of a corresponding dose intramuscularly. This applies to all ocular tissues and not only to the aqueous and vitreous. The effect of adrenalin in reaching and maintaining high intra-ocular levels is more marked with subconjunctival injections than with retrobulbar injections. When doses of 1,000,000 units crystalline penicillin in adrenalin solution 1 :1,000 are injected subconjunctivally, experiments in the rabbit suggest that an adequate level is reached and maintained in both vitreous and aqueous for at least 48 hours. The high level reached and maintained in the vitreous by this dose and mode of administration is particularly noteworthy, for neither massive intramuscular injections nor injections of 50,000 units in adrenalin subconjunctivally give high or persistent levels of penicillin in the vitreous. This dose and mode of administration would appear to render superfluous any direct intravitreal injection of penicillin.

REFERENCES

SORSBY, A. and UNGAR, J. (1946).—*Brit. Med. Jl.*, Vol. II, p. 723.
——— (1947).—*Brit. Jl. Ophthal.*, Vol. XXI, p. 517.
STRUBLE, B. C. and BELLOWS, J. G. (1944).—*Jl. Amer. Med. Assoc.*, Vol. CXXV, p. 685.
TOWN, A. E., FRISBE, E. F. C. and WISDA, J. G. (1946).—*Amer. Jl. Ophthal.*, Vol. XXIX, p. 341.
TOWN, A. E. and HUNT, M. E. (1946).—*Ibid.*, Vol. XXIX, p. 171.

THE CONTROL OF EXPERIMENTAL INFECTIONS OF THE ANTERIOR CHAMBER AND OF THE VITREOUS BY SUBCONJUNCTIVAL AND RETROBULBAR INJECTIONS OF CRYSTALLINE PENICILLIN IN DOSES OF 1,000,000 UNITS

BY

ARNOLD SORSBY *and* JOSEPH UNGAR

LONDON

IT was shown in an earlier study (Sorsby and Ungar, 1946) that infection of the anterior chamber in the experimental animal could be controlled readily by subconjunctival injections of 25,000 units

Each set of two values represents the reading in the right and left eyes of an animal.

penicillin; the application of concentrated ointment, or intramuscular injection of penicillin gave less ready control. Vitreous infections did not respond too well to intramuscular injections, still less to ointment, and whilst subconjunctival injections gave satisfactory results, these were not uniform. The response of vitreous infection to direct intravitreal injection of penicillin was also not too satisfactory (Sorsby and Ungar, 1948). In the present study the effect of doses of 1,000,000 units of crystalline penicillin injected subconjunctivally or retrobulbarly have been investigated in order to determine whether more consistent results could be obtained, and whether the frequency of injection could be reduced. Infection was induced by introducing into the anterior chamber or into the vitreous a suspension of 50,000 staphylococcus aureus organisms in 0·05 ml. of saline.

1.—Infection of the anterior chamber

1. *Treatment by subconjunctival injection.*

Seven adult rabbits were used, of which two were controls. Both control rabbits showed a destructive panophthalmitis within 48 hours. Of the remaining 5, 3 received the first treatment four hours after the infection and two 24 hours after the infection.

(*a*) *Three rabbits first treated four hours after infection.*—These animals received a subconjunctival injection of 1,000,000 units penicillin in 1 ml. water 4 hours after infection, the dose being repeated 20 hours later. The animals therefore received in all two injections. These three rabbits showed slight conjunctival oedema 48 hours after infection, but their corneae were clear. They made an uninterrupted recovery and they were destroyed 12 days after infection, when their eyes were completely normal.

(*b*) *Two rabbits first treated 24 hours after infection.*—In addition to the initial injection of 1,000,000 units 24 hours after infection a further subconjunctival injection of 1,000,000 units was given at 48 hours and at 72 hours after infection. There was considerable cloudiness of the cornea and congestion of the iris when treatment was first instituted and these signs tended to clear progressively. At the end of 10 days the eye of one rabbit was practically normal, and that of the other showed local corneal infiltration with the anterior chamber still somewhat hazy. At 14 days the first of these rabbits still showed blepharospasm and some injection of the conjunctiva, whilst the second now had a definite corneal ulcer with much conjunctival injection and blepharospasm. By 21 days both eyes were relatively normal. In the first rabbit there was a small posterior synechia at 6 o'clock, and in the second there was a small corneal scar.

2. *Treatment by deep orbital injection.*

Four adult rabbits were used and one control. Two rabbits were first treated 4 hours after infection and 2 more 24 hours after infection. The control rabbit showed marked engorgement of the globe within 24 hours and extensive disorganization of the eye after three days.

(*a*) *Two rabbits first treated 4 hours after infection.* — These animals received 1,000,000 units of penicillin in 1 ml. of water 4 hours after infection, and another injection at 24 hours. Of these two, one was completely normal within 24 hours and remained so; the second showed a persistent corneal haze and was destroyed on the 17th day, when the lower part of the cornea was diffusely opaque. A good red reflex was present ophthalmoscopically.

(*b*) *Two rabbits first treated 24 hours after infection.* — A good functional result was obtained in one, the cornea showing little more than a localised scar near the site of the inoculation. The second animal showed extensive corneal haze with considerable iritis.

Judging by the results in this small series, the time at which treatment is initiated is a determining factor for a rapid and uneventful recovery, and subconjunctival injection is probably the better procedure.

2.—Infections of the vitreous

1. *Treatment by subconjunctival injection.*

Five adult rabbits were used, one as the control; two were first treated 4 hours after infection, and two at 24 hours after infection. The control animal showed a grey vitreous reflex within 24 hours.

(*a*) *Two rabbits first treated 4 hours after infection.* — These animals received a subconjunctival injection of 1,000,000 units of penicillin in 1 ml. of water, the dose being repeated 20 hours later. After 24 hours both these rabbits showed externally normal eyes. At 72 hours the corneae were bright and there was a good red reflex ophthalmoscopically in both animals, but some vitreous haze was also present. Forty-eight hours later both these animals were found dead. Post-mortem examination revealed no definite abnormality systemically, and the bisected eyes appeared normal.

(*b*) *Two rabbits first treated 24 hours after infection.*—The first subconjunctival injection of 1,000,000 units penicillin was followed by one more at 48 hours and another at 72 hours. There was considerable congestion of the globe at 20 hours in both animals, and at 48 hours a yellow reflex from the vitreous was present in both animals. At 72 hours the vitreous of one rabbit was an organized grey mass, and of the other an organized yellow mass

with an associated iritis. The subsequent course was a grey reflex from the vitreous in a quiet eye with corneal haze in one animal, and panophthalmitis in the other.

2. *Treatment by retrobulbar injection.*

A series of 8 adult rabbits were used. Three rabbits were used as controls: within 48 hours they showed fairly well established panophthalmitis. When destroyed on the twelfth day their eyes were functionally useless; the corneae were hazy, vascularised and there was much bulbar injection. Of the remaining 5 rabbits three were first treated 4 hours after infection, and in two rabbits the first treatment was 24 hours after infection.

(*a*) *Three rabbits first treated 4 hours after infection.*—One of these received a second retrobulbar injection 24 hours after infection; the two other rabbits had only the first retrobulbar injection followed by four doses of 250,000 units intramuscularly on the second and third day. The first of these rabbits showed an uninterrupted recovery. Of the remaining two, one died on the fourth day after the ocular infection was running a favourable course. The second showed nothing more than a slight iritis with a mild hypopyon on the second day, and by the 12th day the eye had become normal.

(*b*) *Two rabbits first treated 24 hours after infection.*—The first retrobulbar injection of 1,000,000 units of penicillin was followed by one more at 48 and another at 72 hours. By the time treatment was begun there was considerable cloudiness of the cornea, and anterior chamber. On the 10th day both these animals showed a distinct yellow reflex from the vitreous. On the 14th day one showed a corneal ulcer with considerable corneal haze obscuring a view of the interior. In the second animal the cornea and anterior chamber were clear, but the vitreous gave a grey reflex. At 21 days the first animal showed a total vascularised opacification of the cornea; the second with a clear cornea showed a completely organized vitreous.

In infection of the vitreous, as in that of the anterior chamber, the time that the treatment was begun would therefore appear to be one of the determining factors in obtaining a satisfactory response. The available data do not allow a comparative assessment as between subconjunctival and retrobulbar injection.

Discussion

The present study confirms the earlier findings that infections of the anterior chamber can be readily controlled by subconjunctival injections of penicillin in adequate doses. From the study previously published it appeared that with doses of the order of

20,000 units of penicillin injections at intervals of about 6 hours were necessary. The present study suggests that when the infection is not fully established two or three subconjunctival or possibly retrobulbar injections of 1,000,000 units at intervals of 24 hours should control a fairly severe infection of the anterior chamber.

Vitreous infections, which do not give such satisfactory results as infections of the anterior chamber on treatment by subconjunctival injections of relatively small doses of penicillin (of the order of 20,000 units), and do not respond too well to direct intravitreal injection of penicillin, appear to respond to two injections of 1,000,000 units at intervals of 20 hours if treatment is begun sufficiently early. With the dose of infection used in these experiments the results were disappointing if treatment was begun after 24 hours: the results were satisfactory if treatment was begun within 4 hours.

Summary

(1) Experimental infections were induced in the rabbit by injecting into the anterior chamber, or into the vitreous, a suspension of 50,000 staphylococcus aureus organisms in 0·05 ml. saline.

(2) In 9 rabbits the anterior chamber was infected, of these 5 were treated by subconjunctival injection, three receiving their first treatment 4 hours after infection and two 24 hours after infection. Four rabbits were treated by retrobulbar injection, 2 receiving the first treatment 4 hours after infection, and two 24 hours after infection. The three rabbits treated by subconjunctival injection 4 hours after infection made an uninterrupted recovery; the 2 rabbits first treated 24 hours after infection also did well, but the course of the infection was more prolonged, and the sequelae were rather more marked. Of the two rabbits treated 4 hours after infection by retrobulbar injection one made a complete recovery; in the two treated 24 hours after infection, recovery was not so good.

The mode of treatment was 1,000,000 units of crystalline penicillin in 1 ml. of water subconjunctivally or retrobulbarly at each injection. The rabbits treated four hours after infection received a second dose 20 hours later. The rabbits treated 24 hours after infection received subsequent doses at 48 and 72 hours.

The control animals did uniformly badly.

(3) Nine rabbits had intravitreal infection. Four were treated by subconjunctival injection and 5 by retrobulbar injection. The doses and time intervals were essentially similar to those employed for anterior chamber infections. The control rabbits did uniformly badly. The two rabbits first treated by subconjunctival injections 4 hours after infection did well. In contrast, the two rabbits first

treated 24 hours after infection showed disorganized globes. Three rabbits first treated 4 hours after infection by retrobulbar injection also did well, whilst 2 rabbits first treated 24 hours after infection did badly.

We are indebted to Mr. B. Helliwell of the Research Division, Glaxo Laboratories for technical help in the studies recorded in this and the two preceding papers.

REFERENCES

SORSBY, A. and UNGAR, J. (1946).—*Brit. Med. Jl.*, ii, p. 723.
——— (1948).—*Brit. Jl. Ophthal.* This issue, p. 857.

PRELIMINARY NOTE ON THE TREATMENT OF HYPOPYON ULCER BY CRYSTALLINE PENICILLIN IN ADRENALIN IN DOSES IN EXCESS OF 50,000 UNITS INJECTED BY SUBCONJUNCTIVAL OR RETROBULBAR ROUTES

BY

ARNOLD SORSBY *and* JOSEPH UNGAR

LONDON

WHILST the experimental results recorded in the two preceding studies were being established, a parallel investigation was conducted clinically to establish whether the eye tolerates subconjunctival injections of more than 50,000 units of crystalline penicillin and whether the frequency of application could be reduced. The experimental results suggested that higher doses than 50,000 units have the two-fold advantage of giving a higher concentration of penicillin intra-ocularly and that this concentration persisted for longer than with the smaller doses. In an earlier study (Sorsby and Reed, 1947) dosage of 50,000 units of crystalline penicillin in adrenalin at six hourly intervals was advocated. The new experimental data suggested that with injections of 1,000,000 units in adrenalin the intervals might be prolonged to 48 hours.

The following brief notes are recorded to show that at this stage 6 hourly injections of 50,000 units of crystalline penicillin can safely and with advantage be replaced by doses of 500,000 units of crystalline penicillin in adrenalin at intervals of 24 hours.

(1) *Two cases treated by injection of 100,000 units in 0·5 ml. at 12 hourly intervals.*

(*a*) A man, aged 37 years, with an infected corneal ulcer and a minimal hypopyon, showed no intolerance to subconjunctival

injections of crystalline penicillin in doses of 100,000 units in 0·5 ml. of water at 12 hourly intervals. Within 24 hours the hypopyon had gone and injections were continued for three further days.

(*b*) A man, aged 56 years, with an infected corneal ulcer and a hypopyon occupying a quarter of the anterior chamber, likewise showed no intolerance to subconjunctival injections of 100,000 units of penicillin in 0·5 ml. of adrenalin at 12 hourly intervals. He required treatment for 4 days before the hypopyon disappeared.

(2) *Use of 200,000 units at 24 hourly intervals.*

In a case of hypopyon iritis in a woman, aged 29, there was no intolerance—nor any response—to penicillin in doses of 200,000 units in 0·5 ml. of adrenalin at 24 hourly intervals. The injections were discontinued after three days. The iritis and hypopyon subsided slowly on subsequent exclusive treatment by atropine and heat.

(3) *Response to 300,000 units injected at 24 hourly intervals.*

In a man, aged 50, with a severe infected corneal ulcer and hypopyon occupying one quarter of the anterior chamber, the hypopyon disappeared after 5 subconjunctival injections of 300,000 units in 0·5 ml. water administered at 24 hourly intervals.

(4) *Use of 400,000 units at 24 hourly intervals.*

(*a*) In a man, aged 48 years, with a severe infected corneal ulcer, considerable iritis, but only minimal hypopyon, the hypopyon disappeared within 24 hours of a subconjunctival injection of 400,000 units in adrenalin. A second injection of 500,000 units in adrenalin was then given retrobulbarly. Recovery subsequently was uneventful under exclusive atropine therapy.

(*b*) A man, aged 37 years, with a hypopyon in a leucomatous eye, with considerable iritis and no corneal ulcer failed to respond to three subconjunctival injections of 400,000 units penicillin in adrenalin. After a protracted course the condition ultimately subsided. (*This was probably a case of hypopyon iritis rather* than of infection.)

(5) *Use of 500,000 units at 24 hourly intervals.*

These preliminary results have been followed by the use of penicillin in doses of 500,000 units at 24 hourly intervals. In four patients injections in 0·5 ml. adrenalin were used subconjunctivally; in two more the injections were given retrobulbarly.

Three cases treated by subconjunctival injections

(*a*) A boy, aged 17 years, was admitted with a minimal hypopyon, infected ulcer, and mild iritis. There was a history of a

foreign body removed four days previously; the culture showed staphylococci and pneumococci. He was given two injections of 500,000 units penicillin in 0·5 ml. adrenalin at intervals of 24 hours. The hypopyon disappeared within the first 24 hours. There was an uneventful recovery and he was discharged after six days.

(*b*) A woman, aged 34 years, with an old corneal leucoma following scarlet fever in childhood, showed a minimal hypopyon. Within 24 hours after subconjunctival injection of 500,000 units penicillin in adrenalin the hypopyon had almost gone. After two further injections at intervals of 24 hours the lesion had subsided.

(*c*) A man, aged 54 years, was admitted with minimal hypopyon following the removal of a foreign body some days earlier. The culture was sterile. One injection of 500,000 units penicillin in adrenalin subconjunctivally led to the disappearance of the hypopyon within 6 hours.

(*d*) A boy, aged 12 years, developed a hypopyon—rather more than minimal—four days after removal of a corneal foreign body. Two hours after subconjunctival injection of 500,000 units of penicillin in adrenalin, the hypopyon had disappeared. A further injection was given 24 hours later. Recovery was uneventful.

Two cases treated by retrobulbar injection

(*a*) A man, aged 47, showed a hypopyon filling a quarter of the anterior chamber. This followed impaction of a foreign body on the cornea seven days earlier. The conjunctival sac was bacteriologically sterile. There was no response to one dose of 500,000 units penicillin in adrenalin injected retrobulbarly, nor to two subsequent subconjunctival injections of the same dose at 24 hourly intervals. He responded well to a course of sulphamezathine.

(*b*) A man, aged 56, showed a hypopyon filling one quarter of the anterior chamber following the impaction of a foreign body on the cornea nine days previously. A corneal ulcer had developed after the removal of a foreign body: this had been treated in the out-patient department for eight days. On the onset of a rapidly forming hypopyon he was admitted to the wards and the condition cleared completely within 24 hours after a single injection of 500,000 units penicillin in adrenalin retrobulbarly.

The use of 0·5 ml. of adrenalin 1 :1,000 as a solvent is apparently a safe procedure. Some patients are said to be particularly susceptible to adrenalin, and as a precautionary measure it would seem wise, that, where adrenalin is used, the patient's reaction should first be tested by injecting 1 minim of adrenalin 1 :1,000 subcutaneously. Susceptible patients are said to show transient symptoms of collapse.

Summary

(1) The cocainized eye tolerates subconjunctival injections of crystalline penicillin in doses of 100,000 units at 12 hourly intervals and doses ranging from 200,000 to 500,000 units at 24 hourly intervals.

(2) With doses of 500,000 units in 0·5 ml. of adrenalin solution 1 : 1,000, at 24 hourly intervals, preliminary results in hypopyon ulcer are distinctly promising, both as to a satisfactory end result and rapidity of cure.

(3) Though theoretically less efficient, retrobulbar injection of such doses appears to have clinical possibilities.

REFERENCE

SORSBY, A. and REED, H. (1948).—*Brit. Jl. Ophthal.*, Vol. XXXI, p. 528.

ON SYMPTOMS OF THE PULSE IN THE *CENTRAL RETINAL ARTERY*

BY

Professor W. KAPUŚCIŃSKI

POLAND

My "Observations on the pulse and retinal arterial pressure" appeared in the May issue of the *British Journal of Ophthalmology*. The paper was translated from Polish into English in London and printed without my having read the proofs. Unfortunately the translation contains a great number of errors and in consequence parts of the original text have been misinterpreted. Taking advantage of the courtesy of the Editors of the *British Journal of Ophthalmology*, I am presenting here again the main points of my considerations on the problem in question. As my first paper was completed two years ago, and as in the meantime I have had the opportunity to make further observations which induced me to modify to a certain extent my former opinion, especially with regard to the measurements of arterial pressure by Bailliart's method, I consider it essential to take these modifications into account in the present paper.

On direct examination of the fundus oculi we notice two kinds of pulse: one of them I would call the physiological, the other the artificial pulse resulting from pressure on the eyeball. The physiological pulse may be perceived in a certain percentage of eyes examined. The first to describe this pulse was O. Becker[1] in 1872. Limited space does not allow me to submit here a critical review of Becker's observations; suffice it to say that they do not in all instances correspond with the real state of affairs. Ballantyne observed the physiological pulse in all cases which he examined with the aid of Gullstrand's ophthalmoscope. This pulse is based on the following phenomenon: when observing

the S-shaped sections of the off-branchings of the central retinal artery, we notice in them movements which I have called "rebounding movements." These movements occur simultaneously with cardiac systole and consist in a shifting of the bends of the artery in opposite directions. The greater the arterial bends, the more distinct will be these movements which disappear entirely towards the periphery. We do not perceive the phenomenon of dilatation and contraction of the artery which is regarded as an essential feature of the pulse. What then induces me to consider these rebounding movements as the pulse? In order to answer this question it is first of all necessary to explain the mechanism which produces these movements.

Rebounding movements are found in all arteries running an S-shaped course or showing peripheral contraction. Their occurrence can be explained in the following way: at the moment of cardiac systole the blood stream receives an impetus which causes an increase in pressure distributed almost simultaneously throughout the whole arterial system—according to Pascal's law—at an average velocity of 15 m. per second. This pressure disappears in the periphery owing to resistance offered by the viscosity of the blood. In contrast to the great speed with which the pressure is spread, the velocity of the blood stream is very considerably smaller, being only about 1/4 m. per second. The increase in pressure produced by cardiac systole subsides in cardiac diastole. Thus rhythmic changes of the pressure in the arterial system occur: this is the pulse. Outside, the pulse manifests itself by movements of the artery which are visible on its S-shaped bends. In straight running arteries these movements are imperceptible. The changes in pressure which follow the course of the blood stream are manifest only by striking against the bent wall of the artery pushing it thus out of its course, as may be seen distinctly in the arteries of the fundus oculi. When speaking of Pascal's law, I mentioned that pressure is distributed throughout the whole arterial system; this would lead to the conclusion that the lumen of the artery should also dilate under the impetus of this pressure. But such dilatation, which according to the law of physics undoubtedly takes place, is absolutely imperceptible. Neither can it be peristaltic because this dilatation would have to be almost simultaneous throughout the whole arterial system, which is inconsistent with the idea of peristalsis.

In my former paper I quoted publications concerning this problem, therefore I shall not repeat them here. I would only like to mention A. Horst's study on haemodynamics[2], in which the author reviews the entire problem and refers to the literature on the subject.

In short, rebounding arterial movements in the fundus oculi are manifestations of pressure-changes in the blood stream and therefore also of the pulse which reveals itself in the same manner throughout the whole arterial system.

I now proceed to discuss the origin of the pressure pulse. The explanation for this origin given by v. Graefe a hundred years ago is still accepted. Graefe maintained that, on pressure on the eyeball, at a given moment this pressure will be higher than that in the central artery. At the turning-point of both these pressures the blood wave flowing into the artery will still have enough force to overcome this obstacle and to push through towards the periphery. This moment has been regarded as manifesting diastolic pressure in this artery. There is an analogy here with the examination of pressure in the brachial artery. This explanation of Graefe would be correct if the observation of the pressure pulse in the central retinal artery were accurate—*but it is not.* The phenomenon manifests itself differently. If Graefe's statement were indeed true, then the first movement perceived when pressing on the artery would be a dilatation of that artery, whereas the first movement consists in a sagging of its walls. This sagging of the artery is synchronous with cardiac systole, *i.e.,* with increased pressure in the arterial system. However, this sign of sagging of the artery simultaneously with cardiac systole is not the only one which we observe in these conditions. If we increase pressure on the eyeball we observe another phenomenon, namely, the rhythm of the arterial pulse will cease to synchronize with cardiac systole and become alternate, *i.e.,* there will be a dilatation of the artery in the fundus oculi simultaneously with cardiac systole and a contraction of that artery with the diastole. This therefore is the symptom which should be interpreted according to Graefe's theory. It is by no means easy to distinguish these arterial movements or the intervals of this pulsation when exerting pressure on the eyeball. To make this experiment it is absolutely essential that another person should feel the pulse, counting aloud. The experiment is best observed in persons whose pulse is slow, about some 60 beats per minute. When the pulse is quicker, the particular phases overlap and it is difficult to distinguish the moment of their origin.

To sum up, I wish to emphasize once more that in order to understand the symptoms of pressure pulse, it is indispensable to feel simultaneously the pulse of any other artery with the assistance of another person who counts the beats of that pulse.

I discovered this phenomenon of dual phases after the completion of my first article. As it throws new light on the whole

problem I have been compelled to reconsider my opinion published in that article.

What are the conclusions to be drawn from the above-described phenomena? If the first sign appears in the form of sagging of the artery as a result of pressure on the eyeball, then it is certain that this symptom was not produced by the blood stream which overcomes outside pressure exerted on the artery. Nor can it be manifested as an active contraction of the artery, or as a systole, because the artery is incapable of contracting or dilating rhythmically, as assumed by former authors, *viz.*, Graefe and Becker. It is true that the arteries can contract under the influence of the sympathetic nerve, but this contraction will not have the character of a rhythmical movement. The sagging of the artery may be due to an external force, the tension of which changes rhythmically. Such a force is the pulsation in the eyeball due to a rhythmic inflow of blood into the eyeball following cardiac systole. The sagging of the artery therefore would originate in the same manner as the so-called venous pulse. This theory is supported by the symptom of pressure pulsation in a blocked artery, that is to say, in conditions where the flow of blood into the artery is checked.

To summarize, the first sign which becomes manifest when slight pressure is exercised on the eyeball and occurs synchronously with cardiac systole, is produced by an external force, namely, the pulsation of the eyeball. The second symptom, on the other hand, which does not synchronize with cardiac systole when stronger pressure is exerted on the eyeball, occurs in the way described by v. Graefe.

In view of the above, what is to be said of Bailliart's method of measuring central arterial pressure? According to this method, the pressure pulse is the indicator which, however, deviates considerably from the physiological conditions of blood circulation in the arteries of the eyeball, and therefore cannot answer the question concerning the actual systolic and diastolic pressure in the retinal arterial system. Such an answer could only be obtained by a direct examination of the pressure; this experiment was made by Duke-Elder on cats' eyes with the aid of a micromanipulator. Nevertheless, on the basis of Bailliart's method we are able to form an opinion on the pressure in the retinal arterial system, although the results of this method are only of relative value, as are also the results of examining pressure in the brachial artery by way of well-known clinical methods. The indicator for defining the minimal pressure cannot be the first movement of the artery, as Bailliart suggested, but the second which appears alternately with cardiac systole.

Thus when applying Bailliart's method, the pulse of any other artery must be examined simultaneously, and the moment of reversal of the rhythm is to be regarded as the indication of minimal pressure. The difference between systolic and diastolic pressure in the central retinal artery will then be much smaller and will no doubt correspond with the actual state of affairs. Taking into account that in the off-branchings of the central artery rebounding movements are usually accentuated only very slightly, we may assume that the differences in pressure in these arteries will also be very small. It is of no special importance to which artery the measurements by Bailliart's method are applied, as the results can be only relative, although their clinical value will be indisputable.

I believe that the application of this modification of Bailliart's method in determining the indicator will help to eliminate to a considerable extent the disparities in the results obtained by various authors.

BIBLIOGRAPHY

BECKER, O.—*Graefe's Arch. f. Ophthal.*, Vol. XVIII, 1872.
HORST, A.—Problems of Haemodynamics, *Bulletin de la Société des Amis des Sciences de Poznan*, Série B, Livraison VIII, 1947.

A CASE OF PIGMENTED LEIOMYOMA OF THE IRIS

BY

NORMAN FLEMING

LONDON

MRS. S. consulted me on August 15, 1944, with regard to something wrong with her left eye. This proved to be a tumour, involving apparently the whole breadth of the iris and extending over the lower and inner third of its circumference. The growth was encroaching on the pupil, rendering the pupillary margin convex instead of concave in the part involved. In shape the tumour was like a bean and in colour purplish black. The surface was smooth and the margins clearly defined. The growth was in contact with the cornea for about a quarter of its extent and some secondary change in the cornea could be made out.

The patient complained that this mass was increasing in size and becoming dark in colour, that her sight was not so good and that the eye was diverging. This change had been noticed during the past year. The patient's own story leaves one in no doubt

that before that time a swelling of the iris had been present for many years, but the colour had been much the same as that of the rest of the iris. Quite recently I have heard through the patient's father that her mother, who died aged thirty-three when the patient was a baby, had something wrong with one iris, which in his opinion resembled that seen by him in the patient's eye when she was a child.

The growth was so sharply defined that I decided to endeavour to remove it without removing the eye. A conjunctival flap was turned down corresponding to the position of the tumour and an incision, concentric with the limbus and extending for one-third of the circumference, was made in the sclerotic with a Graefe knife. Through this incision, the iris was withdrawn at one end of the tumour, the iris divided, the tumour delivered, and the iris again divided on the other side of the growth. The conjunctival flap was then replaced and stitched. The operation having been successfully performed, the eye healed without any complications.

I have seen Mrs. S. this month (March, 1947). The eye is quiet, corrected vision is 6/5 right and left and she is in the best of health.

The case reported was at first thought to be a malignant melanoma of the iris, but in view of the smoothness of the outline of the tumour and the absence of any evidence of invasion of other tissues, I was in doubt as to whether she should be subjected to deep X-ray treatment or not. I asked Dr. Douglas Webster for his opinion and we decided to ask the opinion of Professor Scarff, Bland-Sutton Institute of the Middlesex Hospital. He reported as follows:—

"I do not think that the appearances indicate melanoma, but rather the tumour usually referred to as leiomyoma of the iris, with included pigment granules."

In addition to expressing my thanks for his report, I have to record my indebtedness to Professor Scarff for the excellent micro-photographs.

No further treatment was undertaken.

There is little to be found in the literature about this very rare tumour and the following résumé is, I think, fairly comprehensive.

In 1898, A. H. Thompson showed a case of Lawford's, a small pinkish cauliflower-like growth of the iris. This was later removed and diagnosed as a spindle-celled sarcoma by all save John Griffith, who contended it was a myoma of the iris and probably a unique growth in that region. It was apparently free from pigment. A drawing of the microscopic structure of the growth is published with the paper which shows clearly that it has much in common with the case here described and with that of Verhoeff.

Only three cases definitely accepted as leiomyomata are

PICTURE 1.

Appearance of the eye before removal of growth.

PICTURE 2.

Appearance of the eye after removal of growth.

recorded. The first is that of Verhoeff, published in 1923, and described by him as a case of mesoblastic leiomyoma of the iris. He states: "the general character of the cells as shown by ordinary stains, together with the presence of myoglial fibrils, leave no doubt that the tumour was a myoma." An unsuccessful attempt to remove it by iridectomy was made in 1904, but a fragment of the tumour, sufficient for microscopical examination, was excised. A second attempt was made in March, 1920, when several fragments of tumour tissue were removed and examined; subsequent enucleation was necessary two months later.

The growth as seen before operation was pinkish in colour. Microscopically tumour cells showed no mitoses, a few branched chromatophores were present near the blood vessels. After sixteen years it did not invade the iris stroma nor did it involve the filtration angle. It arose from the anterior surface of the iris.

The microscopic structure of this growth also is illustrated.

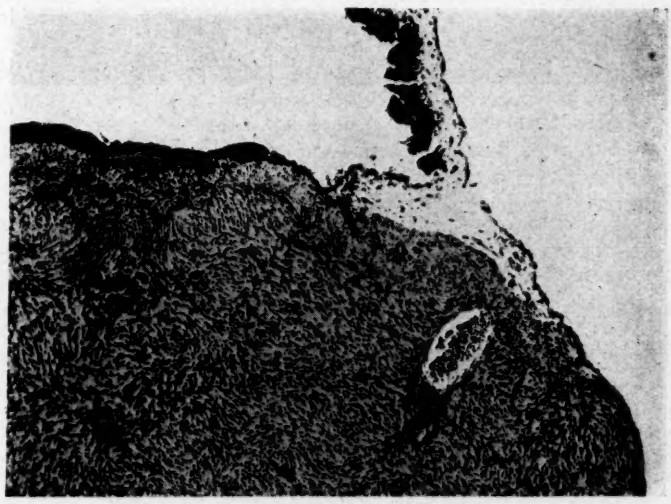


FIG. 1.

Section of the growth magnified ×60.

The second case is that of A. D. Frost, published in 1936. There was a history of two years only. This tumour was yellowish-grey in colour with ectropion of the uveal pigment; it was sessile, and half the width of the iris; the surface near the pupillary border was dotted with pigment. The eye was removed. The growth was

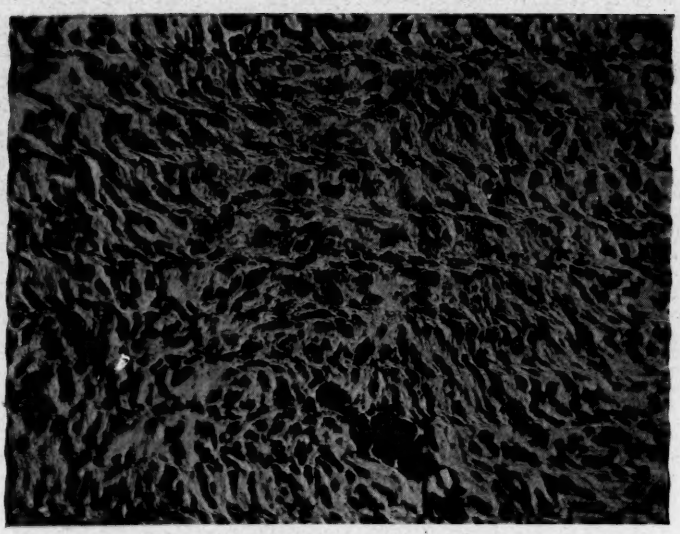


FIG. 2.
Section of the growth magnified ×275.

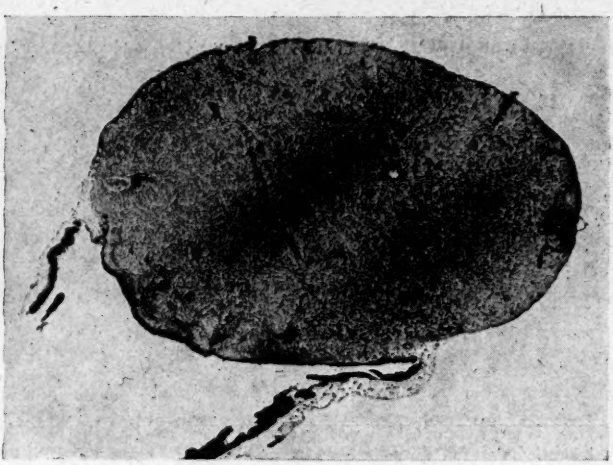


FIG. 3.
Section of the growth magnified ×17.

not pigmented, but a few scattered chromatophores were seen. There were no mitoses. Like Verhoeff, Frost also obtained differential staining with Mallory's phosphotungstic haematoxylin and demonstrates myoglial fibrils by gold impregnation. He comments: "Its outstanding pathologic characteristics include a structure of interlacing closely packed bundles of spindle cells with rod-shaped nuclei in palisade arrangement, displaying eosinophilic cytoplasm and myoglia fibrils."

In Ellett's case in a man of 47 the presence of the tumour had been noted for fifteen years and the iris to have been elongated vertically for five years before that. There is nothing to indicate that the two abnormalities had more than a fortuitous association. It is described as having been light in colour but becoming darker. The eye was enucleated, however, and the growth found to be unpigmented.

It was removed as a sarcoma but diagnosed by Verhoeff as an epiblastic leiomyoma. Verhoeff now considers that the growth arises from the neural epithelium just as does the dilator muscle. He described his case as a mesoblastic leiomyoma in 1923, two year before the publication of Collins and Mayou's Pathology, where it is pointed out that the fibres of the two iris muscles arise from the neural epiblast, whereas the ciliary muscles are mesoblastic in origin.

It would appear that in the case described in the present communication, the tumour was very much larger than in any of the other three; it is unique in that it was heavily pigmented and in that the father's description of her mother's eye strongly suggests a hereditary factor. In the doubtful case of Thompson, the growth was removed by iridectomy by Lawford, but in all three accepted cases the eye was enucleated.

Mr. T. H. C. Benians, who was very interested in this tumour, has kindly given me the following commentary:—

"The four published cases of this condition that may be considered histologically established (*i.e.*, Thompson, Verhoeff, Frost and Ellett), were all in the lower half of the eye, and the same is true of the present case."

From the descriptions and illustrations now available of these five cases there seem to be two types.

In Frost's and Ellett's cases, the growth extends diffusely through almost the whole width (and in Ellett's case the whole depth) of the iris, and the sphincter muscle is involved in both cases. In the other three the tumour projects. Thompson's is described as cauliflower-like. Verhoeff's was attached by a narrow band to the anterior surface of the iris, and in the present case a more or less spherical tumour has its narrow posterior zone sunk

in the substance of the iris. The two last growths definitely have no relation to the sphincter muscle and Verhoeff's appears to rise direct from the anterior pigment layer which constitutes the dilator muscle.

In considering this growth of which only sections were available, I had the advantage of discussing it with Dr. W. M. Woods and we felt that the possibility of it being an unusual form of leiomyoma should not be disregarded. The sections show a piece of iris containing an almost spherical neoplasm (0·4 x 0·3 cm.) which has a very well defined border. A small posterior zone of the neoplasm has replaced both the vessel layer and the anterior border layer of the iris at the site of the neoplasm, so that here only the posterior pigment layer of the iris remains and forms a capsule for the neoplasm posteriorly. The greater part of the neoplasm bulges anteriorly from the iris; its anterior and lateral surfaces are smooth, but show neither capsule nor covering cells. The tumour has a very uniform structure throughout. It is composed of spindle cells, with spindle nuclei and moderately long cytoplasmic bodies. There is very little variation in the morphology of the nuclei and cytoplasm. There is a little imperfect palisading of nuclei. The cells are arranged in a conspicuous regular pattern of bundles; the central cells of each bundle tend to be parallel to one another, while the peripheral cells are curved so that their ends are approximated at opposite poles of the bundle. This is a pattern that is commonly seen in neuro-fibromata, and is quite different from the pattern of leiomyoma of skin or uterus, where all the cells of each bundle are parallel to one another and the bundles are interwoven, so that in any section some bundles show all cells cut longitudinally and others show all cells cut transversely. The cells are not so broad, they have not so much cytoplasm, as the cells of the common pure leiomyoma of the skin, but they contain numerous thick glial fibres, which are characteristic of leiomyoma, but are usually absent from the cells of neuro-fibroma (schwannoma).

Therefore, this tumour has one structural feature that is found in neuro-fibroma and another that is found in leiomyoma. There is much pigment throughout the tumour, but it is mostly in dense clumps and would appear to be some of the normal pigment of the iris included in the tumour tissue, some of it being also in stellate form suggesting its presence in macrophages. Some of the pigment seems to be present in a few of the tumour cells and therefore it may seem justifiable to regard the tumour as a melanotic neuro-ectodermal leiomyoma.

Since one must have a fixed point it might be said first that the presence of myoglial fibres, very clearly demonstrated by Mallory's

phosphotungstic acid-haematoxylin, entitles it definitely to be classified as a leiomyoma. This point is stressed by Verhoeff in relation to two of the three cases he has seen. The general structure of the growth on the other hand has more in common with a neuro-fibroma (schwannoma) than with the ordinary mesodermal leiomyoma and it is to be noted that Verhoeff in two of the cases he has examined draws attention to the palisading of nuclei, a feature very characteristic of schwannoma, though it also occurs sometimes in leiomyoma of the uterus. As to pigment in the four cases already published, and referred to above, pigment appears to have been very scanty and what there was was apparently present in macrophages only so that the question of melanoma did not arise. In the present case, though pigment is very abundant in perivascular spaces, its presence can only be demonstrated in a few of the tumour cells. A somewhat similar picture may be seen in some pigmented neuro-fibromas, where intrinsic pigmentation of tumour cells may be scanty.

Finally, as to the source of such growths. Both sphincter and dilator muscles of the iris have a neuro-ectodermal origin. The sphincter, however, is fully differentiated into muscle bundles, is entirely unpigmented and could presumably give rise to a leiomyoma of classical type. The dilator muscle consists only in a partial differentiation of the outer aspect of the cells forming the anterior of the two pigmented layers covering the back of the iris. A myoma arising from such a source might not unreasonably be expected to show features linking both nervous and muscular characters, and such a mixture of characters does seem to be present in the tumour here described. A likely ectodermal character in such a growth would also be the intrinsic production of pigment and that appears to be occurring in this case though it definitely was not a feature of the other published cases. It is to be noted that Reese (1947) classifies leiomyoma of iris as a pigmented tumour.

To sum up what has been said, we felt that this group should not be classified off hand as leiomyoma of neuro-ectodermal muscle but the point should be kept open as to whether this tumour and some others, such as that of Verhoeff, do not present characters that make their classification as leiomyoma as anomalous as that of the neuro-ectodermal musculature from which they appear to derive.

Muscular and pigmentary functions co-exist in the dilator muscle cells and it might be that further degrees of muscular differentiation, corresponding to that seen in the sphincter iridis muscle, would definitely exclude the melanoblastic function. A failure in the specific myoglial differentiation in a growth from this source

could lead to the production of a spindle celled melanoma and no doubt the question of malignancy would be closely bound up with these types of differentiation."

BIBLIOGRAPHY

ELLETT, E. C. (1939).—*Arch. of Ophthal.*, Vol. XXI, No. 3, p. 497.
FROST, A. D. (1936).—*Trans. Amer. Ophthal. Soc.*, Vol. XXXIV, p. 86.
REESE, A. B. (1947) —*Amer. Jl. of Ophthal.*, Vol. XXX, No 5, p. 37.
THOMPSON, A. H. (1899).—*Trans. Ophthal. Soc. U.K.*, Vol. XIX, p. 19.
VERHOEFF, F. H. (1923).—*Arch. of Ophthal.*, Vol. LII,. No. 2, p 132.

OBSERVATIONS ON EXPERIMENTAL PNEUMOCOCCAL INFECTION OF THE RABBIT'S CORNEA AND ON THEIR TREATMENT WITH PENICILLIN*

BY

J. MACASKILL *and* M. WEATHERALL

EDINBURGH

THE experimental production of infected lesions of the rabbit's cornea by intra-corneal inoculation of suspensions of pneumococci has been described by Ginsberg and Kaufman (1913) and by Robson and Scott (1943*a*, *b*). Cole, Hamilton-Paterson and Sorsby (1945) were unable to confirm the findings of Robson and Scott, although they used the same strain of pneumococcus. This divergence of results has not, as far as we know, been explained (Fraser, Robson, Scott and Scott, 1945; Sorsby, 1946). The present paper reports further observations on the lesions produced by intra-corneal inoculation of the same and other strains of pneumococci and on the effect of penicillin administered subconjunctivally on these lesions. It is by now well known that bacteriostatic concentrations of penicillin can be produced in the aqueous and cornea by subconjunctival injection of suitable doses (Andrews, 1947; Leopold and La Motte, 1945; Sorsby and Ungar, 1947; Struble and Bellows, 1944; von Sallmann, 1945). The present observations are directed to show whether this route of administration is in fact as well as in expectation therapeutically efficient, and if so, under what conditions.

Methods

Young rabbits of both sexes weighing 1·0 to 1·8 kg. were used. Intra-corneal injections were performed as described by Robson

* From the Department of Pharmacology, University of Edinburgh. Received for publication, September 11, 1948.

and Scott (1943*a*) under intravenous thiopentone anaesthesia (approximately 25 mg./kg.) except in one experiment in which intravenous pentobarbitone (approximately 30 mg./kg.) was used. A twenty-four hours culture of pneumococci in plain broth was used throughout. Treatment was applied at various times as described in the section on results. Subconjunctival injections were made under the bulbar conjunctiva near the limbus, without anaesthesia, as the rabbits tolerated this procedure well. The eyes were observed daily for the first few days and less often later. Pure penicillin, kindly supplied by Mr. Beal, of Imperial Chemical Industries (Pharmaceuticals), Ltd., was used, freshly dissolved in sterile 0·9 per cent. sodium chloride solution. Some control animals were treated with subconjunctival sodium chloride, some with subcutaneous penicillin, and others received no treatment. No appreciable difference was found between the two groups which did not receive penicillin, and they will be considered together.

Results

(1) *Untreated Cases.*—The lesions observed have been of variable severity but fairly constant in type. In the most satisfactory experiments, twelve hours after inoculation, little was to be seen except the mark of the needle and some opacity where the bleb of material had been deposited. By twenty-four hours, this area had become oedematous and infiltrated, and the conjunctiva was congested and a muco-purulent discharge was present. In the next day, the infective infiltration of the cornea extended greatly: iritis often appeared and the conjunctival discharge usually increased. Hypopyon commonly appeared on the third or fourth days, and after this time little increase in the reaction took place. After ten days or so in some cases, and less in milder ones, the lesions began to resolve, leaving a corneal scar sometimes just discernible and sometimes up to 5 mm. in diameter.

Lesions which followed this pattern were not always produced (Table I). In all, five strains of pneumococcus were tried, three of type XIX and one each of type III and type XXIII. One of type XIX, the strain used by Robson and Scott, in our hands consistently produced lesions of the type described when used in a dilution of 10^7 organisms per ml. The type III organism in a dilution of 10^5 organisms per ml. produced in eight out of fourteen eyes inoculated at the same time lesions which at thirty-six hours appeared particularly severe, in one eye a moderate lesion, and in five eyes in three rabbits no lesion at all. The other strains in dilutions from 5×10^4 to 10^9 organisms per ml. produced mild

TABLE I

Results of intracorneal inoculation of various strains of pneumococci

Organism	Strength of suspension, orgs/ml.	No. of rabbits	No. of eyes	Mean severity of untreated lesion		
				2nd day	4th day	9th day
Type III	10^5	7	9	3†	†	†
			5	0	0	0
Type XIX (A) ...	10^7	2	4	2	3	$3\frac{3}{4}$
,,	,,	3	6	$1\frac{2}{3}$	$2\frac{1}{2}$	$3\frac{1}{3}$
Type XIX (B) ...	5×10^4	1	2	Mild	Mild	0
,,	5×10^6	1	2	,,	,,	0
,,	5×10^8	1	2	,,	,,	0
Type XIX (C) ...	5×10^5	2	4	0	0	0
Type XXIII ...	10^6	1	1	2	$\frac{3}{4}$	0
,,	10^9		1	$2\frac{1}{2}$	$\frac{3}{4}$	0
Type III	10^6	2*	2	Fatal	in 36	hours.
Type XIX (C)	10^6		2	,,	,,	,,

NOTES :—(A), (B), (C). Three different strains of type XIX, as described in the text. (A) is the strain previously investigated by Robson & Scott (1943*a*, *b*) and by Cole, Hamilton-Paterson and Sorsby (1945).

† Value at 36 hours. Treated thereafter with penicillin (group C of table II).

* Each rabbit injected with type III in one eye and type XIX (C) in the other.

lesions, apparently independent of dose and healing in a few days. The last were too mild to show clear-cut responses to treatment and were not studied further. Therefore, only the original strain of type XIX produced lesions with sufficient constancy for satisfactory evaluation of therapeutic procedures: the eyes infected with the type III organism were, however, also treated at a later stage, with results striking enough to deserve mention.

(2) *Effects of treatment.*—Three groups of experiments were performed. In each group, five to eight rabbits were infected in both eyes at the same time. Some were used as controls, some were treated with penicillin subcutaneously and some subconjunctivally. The selection of animals for different groups was performed by a random process and without regard for the state of the lesion. The schemes of treatment are shown in Table II.

TABLE II

Schemes of Treatment

Experimental group ...	A	B	C
Pneumococcus type ...	XIX	XIX	III
Amount of penicillin given at each injection ...	10,000 u/kg.	1,000 u/kg.	1,000 u/kg.
Subconjunctival penicillin given at (hrs. after inoculation) R. eye	12, 24, 36, 48	12, 24, 36, 48	36, 48, 60
Subconjunctival penicillin given at (hrs. after inoculation) L. eye	24, 36, 48	24, 36, 48	36, 48, 60
No. of rabbits	2	3	3
Subcutaneous penicillin given at (hrs. after inoculation)	12,24*,36*,48*	12,24*,36*,48*	None
No. of rabbits	1	2	2
Untreated or treated with subconjunctival saline. No. of rabbits	2	3	0

* Double dose, corresponding to the total amount of penicillin given subconjunctivally.

The severity of the lesions observed was scored on an arbitrary scale as follows: The corneal lesion was graded as mild, moderate or severe, and scored 1, 2 or 3 accordingly. Iritis and hypopyon were graded as slight or severe and each scored $\frac{1}{2}$ or 1 accordingly. The total score was summed for each eye. In this way weight was attached mainly to the corneal lesion, but independent cognisance was taken also of the reaction by the deeper parts of the eye. Two observers made independent readings and the average was taken. The mean results for all the eyes on each treatment in each group are shown in Figs. 1-3. The number of observations is too small to afford an accurate estimate of the variation, but individual values nearly all lay within the range of $\pm$ 50 per cent. of the observed means.

It will be seen that with doses of 10,000 units/kg. there was little difference in the effects of systemic and local penicillin. Even though the drug was administered as infrequently as twelve-hourly, the infection was completely arrested within four days, while the controls were still deteriorating after a week. When the dose used was 1,000 units/kg. it was practically as effective

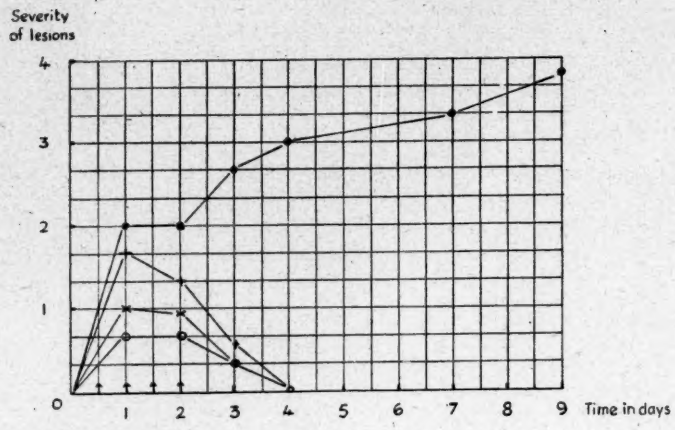


FIG. 1.

Effect of large doses of penicillin on corneal lesions produced by pneumococcus type XIX (experimental group A). Ordinates, severity of lesion in arbitrary units as described in text. Abscissae, time in days from inoculation. Arrows indicate administration of penicillin, 10,000 units/kg. body weight.

●——● Solid circles, no penicillin (4 eyes).
O——O Open circles, penicillin subcutaneously (2 eyes).
×——× Oblique crosses, penicillin subconjunctivally starting at the first arrow (2 eyes).
+——+ Vertical crosses, penicillin subconjunctivally starting at the second arrow (2 eyes).

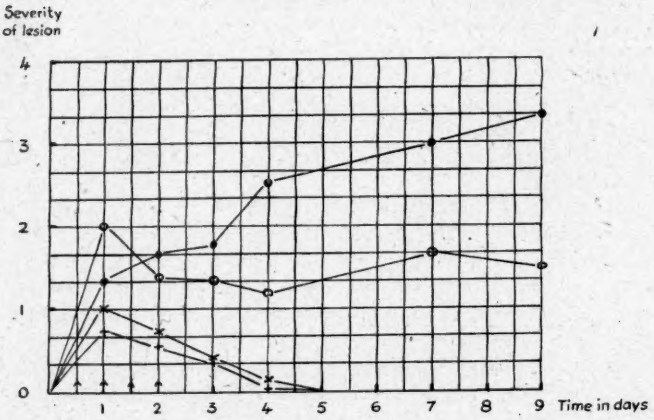


FIG. 2.

Effect of small doses of penicillin on corneal lesions produced by pneumococcus type XIX (experimental group B). Ordinates, abscissae and symbols as in Fig. 1. Penicillin 1,000 units/kg. body weight in each dose. Six, four, three and three eyes in respective groups.

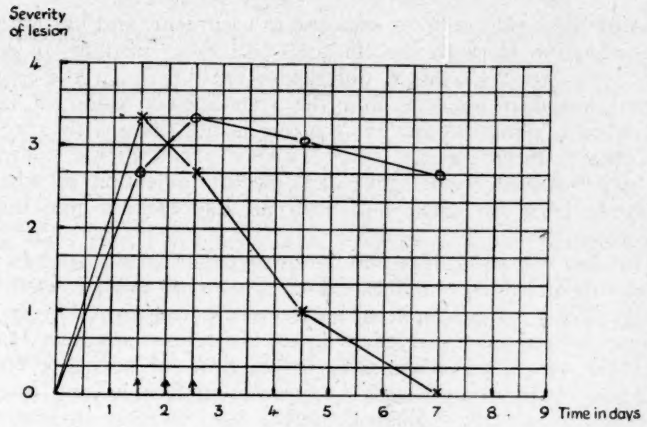


FIG. 3.

Effect of small doses of penicillin on corneal lesions produced by pneumococcus type III (experimental group C). Ordinates, abscissae and symbols as in Fig. 1. Penicillin 1,000 units/kg. body weight in each dose. Six eyes treated subconjunctivally and four subcutaneously.

as the larger dose if given subconjunctivally. Subcutaneously this dose appreciably mitigated the severity of the infection but not unexpectedly was insufficient to produce a cure. This distinction applied equally to treatment started at 12-24 hours (group B) and when it was delayed until lesions were well established (group C).

Discussion

Several points of interest arise from these observations. First, the untreated lesions with the type XIX organism used by Robson and Scott and by Cole *et al.* differ somewhat from those previously reported. On the whole, they resemble those described by Robson and Scott (1943*b*), but are perhaps better described as infective lesions of the substantia propria of the cornea than as corneal ulcers. Cole *et al's* (1945) description of their lesion after intra-corneal inoculation of this strain suggests that in their hands a much milder lesion was obtained, probably similar to those reported here with other strains of type XIX and with a strain of type XXIII. There is evidently much variation in the responses produced at different times and by different strains, without obvious reason.

The type XIX lesion has been used in these experiments because in our hands it has been of sufficient constancy and

duration to show a definite response to treatment, and has allowed discrimination between the efficacy of different methods of treatment. As always, certain differences exist between the experimental lesion in animals and the spontaneous lesion in man; and what is demonstrable for the one is not necessarily true for the other. Nevertheless, until evidence arises to the contrary, the experimental results provide a useful indication of what is likely to occur in man, and with all due caution may be so interpreted.

The data presented leave no doubt that the lesion responds well to treatment with penicillin. The system of dosage used was hardly likely to maintain a bacteriostatic concentration in the cornea and was not intended to do so. Injections at twelve-hourly intervals were used deliberately to see how far adequate results could be obtained with such a clinically preferable long interval between treatments. Zubrod (1947) has recently shown that survival in mice infected with β-haemolytic streptococci and treated with penicillin G depends mainly on the total dosage and is not increased by giving penicillin more than once in twenty-four hours; and, as Marshall (1948) has pointed out, the assumption that a maintained bacteriostatic concentration is necessary for effective therapy remains unproven. The present experiments are consistent with the hypothesis that it is unnecessary, or at least not altogether necessary.

It is also apparent that subconjunctival administration is substantially more effective than systemic administration, particularly when doses comparable to those used in man are employed. This conclusion is supported by the results one of us (J. M.) has seen in treating septic ulcers of the cornea in man, and by the recently published clinical account by Sorsby and Reed (1947).

Summary

The responses of rabbits to intra-corneal injections of various strains of pneumococci are described. The lesions were variable, but with one or two strains keratitis, iritis and hypopyon were produced with sufficient constancy to permit the evaluation of therapeutic procedures. Penicillin was found to be more effective when administered subconjunctivally than subcutaneously, and by the former route completely to arrest infection when 1,000 units per kg. body weight was given at twelve-hour intervals.

Acknowledgments. We are indebted to Dr. J. P. Duguid for much helpful discussion and for providing the cultures of pneumococci; to Dr. J. M. Robson for collaboration in certain

preliminary experiments; to Miss Irene Munro for technical assistance; to the W. H. Ross Foundation (Scotland) for the Prevention of Blindness for defraying the expenses of this work; and to Imperial Chemical Industries (Pharmaceuticals), Ltd., for a generous gift of pure penicillin.

REFERENCES

ANDREWS, G. W. S. (1947).—*Lancet*, i, p. 594.
COLE, W. T. S., HAMILTON-PATERSON, J. L. and SORSBY, A. (1945).—*Brit. Jl. Ophthal.*, Vol. XXIX, p. 150.
FRASER, I. C., ROBSON, J. M., SCOTT, A. A. B. and SCOTT, G. I. (1945).—*Brit. Jl. Ophthal.*, Vol. XXIX, p. 667.
GINSBERG, S. and KAUFMANN, M. (1913).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LI, p. 804.
LEOPOLD, I. H. and LAMOTTE, W. O. (1945).—*Arch. Ophthal.*, Vol. XXXIII, p. 43.
MARSHALL, E. K., JR. (1948).—*Bull. Johns Hopkins Hosp.*, Vol. LXXXII, p. 403.
ROBSON, J. M. and SCOTT, G. I. (1943*a*).—*Lancet*, i, p. 100.
——— (1943*b*).—*Brit. Jl. Exp. Path.*, Vol. XXIV, p. 50.
SORSBY, A. (1946).—*Brit. Jl. Ophthal.*, Vol. XXX p. 64.
SORSBY, A. and REED, H. (1947).—*Brit. Jl. Ophthal.*, Vol. XXXI, p. 528.
SORSBY, A. and UNGAR, J. (1947).—*Brit. Jl. Ophthal.*,, Vol. XXXI, p. 517.
STRUBLE, G. C. and BELLOWS, J. G. (1944).—*Jl. Amer. Med. Assoc.*, Vol. CXXV, p. 685.
VON SALLMANN, L.—*Arch. Ophthal.*, Vol. XXXIV, p. 195.
ZUBROD, C. G. (1947).—*Bull. Johns Hopkins Hosp.*, Vol. LXXXI, p. 400.

SCLERAL DEGENERATIONS:—
A case of scleromalacia perforans*

BY

Dr. S. N. MITTER

DELHI

DEGENERATION and deficiencies of the sclera have rarely been described in detail. They occur more frequently, but they are not noted as often as would a similar corneal lesion be noted. Rones[1] in an extensive survey says that senile degenerations in the sclera are chiefly fatty infiltrations. Duke-Elder[2] states that fatty and hyaline degenerations are fairly common in old age. Calcification is also common as a senile degeneration and as a terminal event in post-inflammatory fibrosis. There is no reason, however, to believe that these degenerations are necessarily limited to old age, as is shown by Coats's case of amyloid degeneration in a man aged 27 years.

Graves[3, 4, 5] first described in detail superficial deficiencies of the

* Received for publication, June 28, 1948.

sclera which were bilateral. On the mesial side of the cornea near the insertion of the internal recti are small areas of slate grey colour with sharply demarcated border, about 2 mm. by 1 mm. on an average and situated about 3 mm. away from the limbus. The optical appearance resembles a squared hole on the outer layers of the sclera and the grey colour is due to the ciliary body shining through it. There is an abrupt step-like limitation of this thin area of the sclera. He at first thought that the condition was only mesial, and developmental in origin. He revised his opinion later when such defects were noted even in the lateral side of the eyeball. Culler[6] made an extensive study of the pathology of these defects to which he gave the name of scleral plaques. A plaque examined histologically was found to contain globules filled with granular débris lying immediately under the epithelium. At the edge of the lesion the sclera was 0·6 mm. thick, whereas in the centre it was only 0·3 mm. thick. The granular débris was entirely free from cellular structure and contained large masses of hyaline. There were no calcium deposits. Surrounding this degenerated area was a zone of about 0·5 mm. broad in which connective tissue fibres appeared to be swollen, presumably from degeneration.

Graves'[3, 4, 5] and Culler's papers clearly describe a type of scleral degeneration. It has been suggested that these lesions are areas of localized hyaline degeneration. The areas are definite and discrete, and fairly well circumscribed. The cases described by them have all been in elderly patients, average age 70 years, and most of them have not been accompanied by inflammatory signs.

Van der Hoeve[7] described in detail another type of scleral degeneration which he named scleromalacia perforans. Duke-Elder[2] emphasises that perforation in this disease occurs without any dominant sign of inflammation, and that the condition may drag on for years without doing much damage or exciting many symptoms. It was considered by van der Hoeve that such perforations occurred in already degenerate or deficient areas of the sclera.

There are, however, important reasons to believe that scleromalacia perforans is essentially a separate clinical entity. It occurs in comparatively young people, who almost always give a history of rheumatoid arthritis. It is preceded by the formation of nodules on the sclera, which later on perforate to give it the appearance of a cystoid scar. The congestion round the nodule is very moderate and signs of inflammation inside the eye are seldom present. Iris or other uveal tissue may be herniated through these perforations, and epithelium is seldom broken over such areas. The whole process takes a long time, sometimes several months or over a year. These nodules are never seen in the other type of degeneration, nor are the plaques known to perforate or to occur in any other place

excepting mesial or lateral sides. The formation of these nodules has been compared to the formation of subcutaneous nodules in cases of rheumatoid arthritis. Metabolic changes are supposed to take place in the sclera resulting in the deposition of some chemical substance. Necrosis takes place in this sharply defined area, which becomes surrounded by a wall of epithelioid cells. Pus cells gradually infiltrate into this area until it becomes completely disintegrated. When perforation occurs this sequestrum is discharged, and the necrotic tissue may be replaced by a fibrous mass.

Rochat first described this condition under scleritis necroticans; van der Hoeve[6] then studied four cases, two of his own and two of Prof. Rochat's; Verhoeff and King[8] later collected and reviewed fourteen cases, and most of our knowledge is derived from these authors. Arkle and Ingram[8] have subsequently described another case in a woman aged 34 years whom they observed for more than three years. It has been difficult for me to trace any other reference in the literature available here. For the last four years I and my colleagues have been on the look out for this condition in a hospital of 20,000 new outpatients a year, but we failed to detect more than one case. These facts go to show that the condition is rare, and the following case observed for four years is, therefore, worth recording:—

R.S., male, aged 24 years, attended hospital on June 5, 1942. One month previously, while cycling in a torrid sun, he felt pain on the left forehead, and since then has had dimness in the left eye.

He had several medical examinations done, the last in May, 1941, when his vision in both eyes was normal. He is of active habits and as an overseer in Government employ has to do much touring work in the sun; thinly built with a dry skin, large scar mark below the mandible on the left side; as a child he had "glands in the neck," and the mark was the scar of an operation performed by a surgeon then; no lymphadenitis now; definite history of a prolonged illness in which there was pain and swelling of the joints; no history of tuberculosis in the family. He was married at the age of fourteen and has two children, both healthy; not addicted to any intoxicant, and is a strict vegetarian. Blood W.R. negative. On examination R.V. 6/4·5, no abnormality; L.V. was 6/24—pupil slightly dilated and sluggish; media clear; inner and upper margin of the optic disc seemed blurred, but there was no haemorrhage either on the disc or in the fundus. Retrobulbar neuritis? Blood W.R. negative. Patient was put on potassium iodide and vitamin B internally and dionine locally. Rapid improvement followed, and by July 18, 1942, vision was 6/9 and the disc looked normal.

Shortly after that he discovered that he had a small hair-like

line of blue shade in the lower part of the eye near the cornea; this had developed between July 8, 1942, and July 18, 1942. On examination it was found that an area about 2 mm. wide extending from " 4 o'clock " to " 8 o'clock " on the limbus appeared to be oedematous; no vascularization, no watering; conjunctiva over the area appeared to be stretched and thinned out; vitreous clear, and fundus condition remained the same as on July 8, 1942. This raised patch, which had a soft cystic texture, grew fairly rapidly and developed a yellowish look. The surface appeared granular, and resembled a patch of xerosis. Vision went on improving till it was 6/3 on September 3, 1942. Patient was put on vitamins internally and haliverol locally. It was of interest to note that the vision had improved in spite of the growth of the patch. Tension was 18 (Schiötz).

He came again on May 19, 1943. Examined on that day his R.V. was 6/4·5 and the eye showed no abnormality. His left vision was 6/36, the patch had grown more cystic and was resembling a filtering cicatrix which one sees after a sclero-corneal trephining, except that the present bleb covered a larger area. Folds had appeared in Descemet's membrane below, radiating from the " 6 o'clock " area and extending to about the middle of the cornea, and these seemed to alter with the movement of the globe. The anterior chamber was shallower in the lower portion; viewed from the upper half the media looked clear, disc margin still slightly blurred. The tension which was normal last year was now 8 (Schiötz). With +1·0 D. cyl. axis 90° vision was improved to 6/12. It was evident that the sclera had perforated underneath the bleb and the subsequent picture was due to this. He was given glasses, and intensive constitutional treatment with vitamin B complex and calcium was prescribed. Atropine and dionine were also used locally.

He was seen on April 17, 1944, by two colleagues at Lahore. One said it was " fatty degeneration of the sclera close to limbus "; the other thought that " it was a degeneration of the cornea and sclera at the limbus."

He returned again on August 1, 1946, complaining that vision was steadily deteriorating in the left eye. On examination Right Vision was 6/4·5—no abnormality noted. The left eye showed the following: V. . . . 4/60, pupil dilated and fixed (the patient had been using atropine off and on), retinoscopy $-\!\!\left|\begin{matrix}+7.5\\ \bigcirc\end{matrix}\right. \bar{c} \frac{0.50}{+6{\cdot}0\,/_{70}}$ V=6/24. The cystic swelling had extended; its largest area of breadth was about 4 mm. at " 7 o'clock." At " 7 o'clock " there is a linear conjunctival fold, and through the thin portion is seen a

darkish area with a yellow fringe. On the inner side the fold becomes continuous with the sub-conjunctival tissue which is slightly vascularised, and is slightly raised up to the fold. The cornea in the lower portion was looking slightly flat; the folds in Descemet's membrane had increased. Pupil was circular, no posterior synechia, no " K.P."; punctate opacities of the lens could be seen in the equatorial area. Disc presented the same slightly blurred appearance as before, but finer details of the fundus could not be made out. The tension was so soft that the tonometer needle did not move. A drawing of the eye on this

FIG. 1.

occasion is given. It was obviously shrinking, and markedly contrasted with the healthy right eye.

A condition has been described in a patient aged 27, with a definite history of rheumatoid arthritis, in whose eye a small cystic swelling occurred near the limbus in July, 1942; till May, 1943, vision and tension remained normal, though the swelling appeared to extend. Then a perforation into the anterior chamber occurred, followed by a remarkable fall of tension. Although the tension remained low through four years, vision with glasses was still 6/24 in 1946. There was no history of trauma, and an implantation cyst of the sclera could be ruled out. The retrobulbar neuritis was

possibly a deficiency phenomenon and responded rapidly to vitamins, but for the scleral lesion no treatment availed. There was no sign of uveal inflammation or vascularization, and the condition was due to a degeneration of the sclera causing perforation and subsequent hypotony.

REFERENCES

1. RONES.—Senile changes and degeneration in the human eye. *Amer. Jl. Ophthal.*, Vol. XXI, No. 3, p. 243, 1938.
2. DUKE-ELDER.—Text-book of Ophthalmology. Vol. II, p. 2066, 1946.
3. GRAVES.—Bilateral mesial superficial deficiency of sclera. *Brit Jl. Ophthal.*, Vol. XXI, p. 534, 1937.
4. ——— Bilateral mesial superficial deficiency of sclera—scleral plaques. *Brit. Jl. Ophthal.*, Vol. XXIII, p. 191, 1939.
5. ——— Bilateral mesial deficiency of the sclera—scleral plaques. *Brit. Jl. Ophthal.*, Vol. XXV, p. 35, 1941.
6. CULLER.—The pathology of the scleral plaque. *Brit. Jl. Ophthal.*, Vol. XXIII, p. 44, 1939.
7. VAN DER HOEVE.—Scleromalacia perforans. *Arch. f. Ophthal.*, Vol. XI, p. 111, 1934.
8. ARKLE and INGRAM.—? Scleromalacia perforans. *Trans. Ophthal. Soc. U.K.*, Vol. LV, p. 552, 1935.
9. VERHOEFF and KING.—Scleromalacia perforans (as referred to by Culler). *Trans. Amer. Ophthal. Soc.*, 1938.

TECHNIQUE OF IRIDENCLEISIS*

BY

L. WEEKERS *and* R. WEEKERS

LIÉGE, BELGIUM

IN various papers (1 to 11), since 1931, in collaboration with our colleagues Hubin, Fanchamps, Bonhomme, Heintz, Mathieu, Roussel, Gérard, Thibert, we have maintained that iridencleisis is the best anti-glaucomatous operation. It reduces the level of intra-ocular pressure more than any other operation, it is the least mutilating, and it can be used in all types of glaucoma.

Because traumatic iris prolapse may be followed by hypertension rather than hypotension, it is important that the technical details of iridencleisis be discussed. The placement, length and direction of the scleral incision; involvement of iris and ciliary body in the scar; changes in the anterior chamber angle and Schlemm's canal; all may influence the tensional results of surgical intervention.

Inasmuch as various methods of performing iridencleisis are not

* Received for publication, June 5, 1948.

equally effective, it is necessary to discover that which affords the most consistent and lasting results, which is the least traumatizing, and that which bears the least complications.

The technique described below has been used now for the last 18 years in hundreds of cases, substantially without modification. It is so simple that it is difficult to imagine any way of making it still easier.

Pre-operative preparation

One of the important advantages in this method of performing iridencleisis is that prolapse of the iris, during the operation, is spontaneous. Other methods, particularly that of Holth, depend on the manoeuvre of catching the iris with a hook or with forceps.

Because either a very miotic pupil or a very dilated one may prevent this spontaneous prolapse, the use of miotics is discontinued on the evening before surgery. Even when the intra-ocular pressure in the fellow eye may be normal, this eye is kept under miotics as a preventive measure.

On the evening before surgery and on the day of surgery a solution of penicillin (1,000 U. per c.c.) is instilled frequently in both eyes.

Anaesthesia

One hour before operation, the patient is given a subcutaneous injection of 0·5 c.c. of scophedal (eucodalscopolamine). Just before surgery a retrobulbar injection of 1 c.c. of a mixture of 4 per cent. novocaine and one drop of 0·1 per cent. epinephrine is given. The epinephrine tends to dilate the pupil but has the advantage of reducing intra-ocular pressure.

In order to avoid the mydriasis caused by cocaine, a 2 per cent. solution of butelline is instilled for topical anaesthesia. A few drops of 2 per cent. novocaine without epinephrine are injected into the conjunctiva of the upper fornix. It is advisable to avoid injection near the limbus because of consequent oedema.

Operation

(*a*) *Dissection of the Conjunctiva* (Figs. 1 and 2).—A tension suture is placed in the conjunctiva at twelve o'clock, about 15 mm. above the limbus. The assistant can raise the conjunctiva away from the tendon of the superior rectus muscle by means of this suture.

The incision is begun above with scissors and penetrates to the sclera to insure a thick flap. A thin flap is thought to be a cause

for late infections reported by many using such filtering operations as the Elliot trephining procedure.

The incision may be continued with a cataract knife nasally and temporally to the horizontal limbus. It is helpful to fixate the eyeball by means of a snap forceps on the tendoninous insertion of the superior rectus muscle. This makes dissection of the flap easier and more precise and prevents tearing of the conjunctiva.

The dissection is carried into the limbus from 10 around to 2 o'clock, far enough so that corneal tissue becomes visible. When the flap is completed it should drape over the cornea spontaneously.

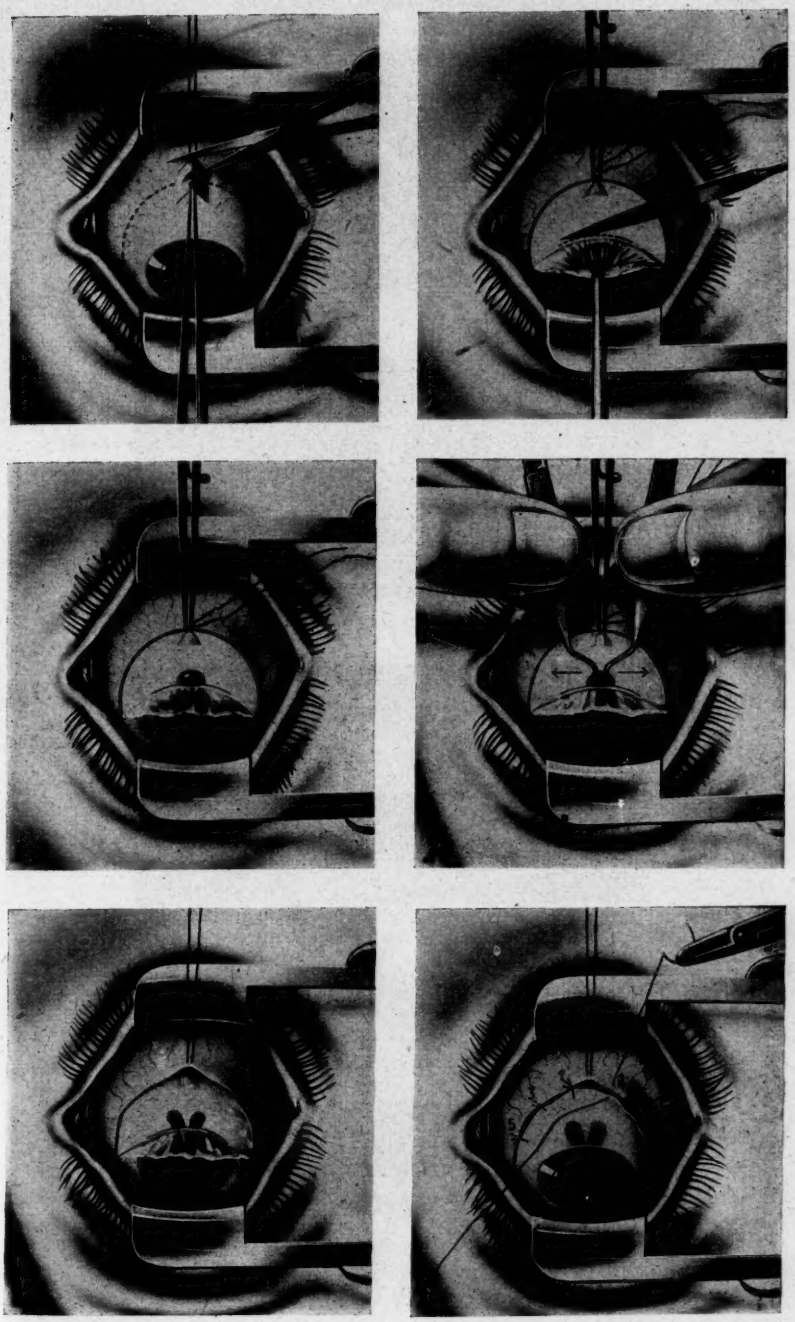
(*b*) *Incision in the Eyeball* (Figs. 2 and 3).—Whereas for dissection of the conjunctival flap the cataract knife was used in a tangential manner, for the incision into the eyeball it is applied perpendicularly to the globe. Firm fixation of the eyeball is maintained by the assistant. After marking, just within the limbus at 12 o'clock, the incision is completed with one bold stroke of the knife. As a result of the sudden opening of the eyeball, aqueous spouts through the wound, carrying with it the iris. This spontaneous prolapse occurs even in the presence of posterior synechiae or even in the presence of a completely secluded pupil. The sudden rush of aqueous tears any adhesions present.

If the operator is too cautious in making the incision, aqueous escapes slowly and spontaneous iris prolapse may not occur. However, light pressure on the eyeball in a nearby area is usually sufficient to prolapse the iris into the wound so that it can be grasped with a forceps.

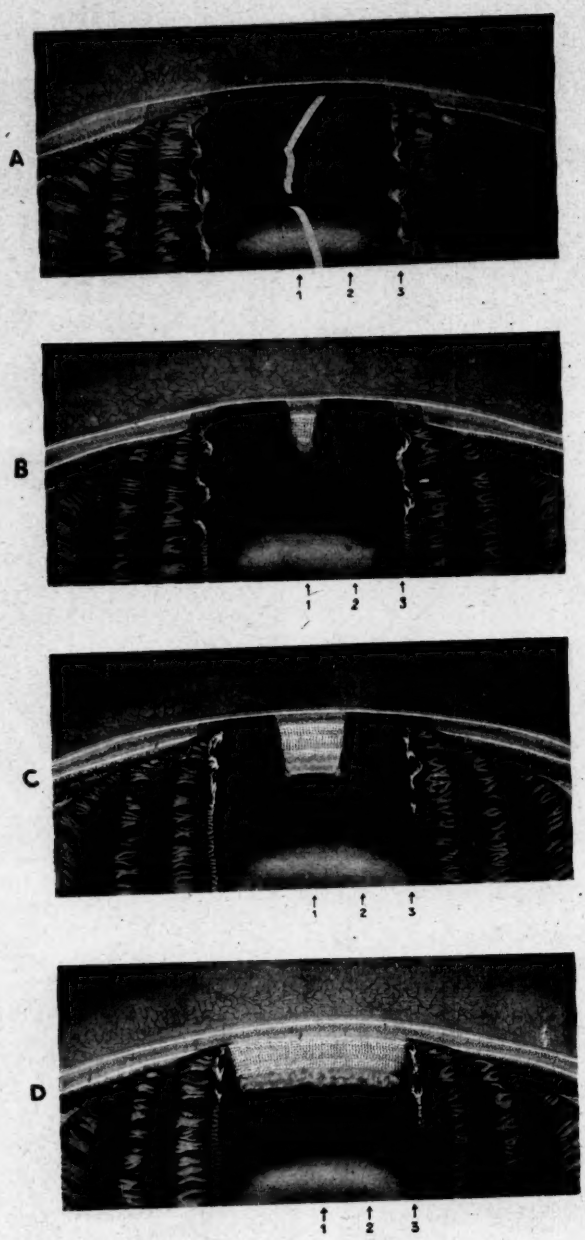
(*c*) *Tearing of the Iris* (Figs. 3, 4 and 5).—The iris prolapse appears in the incision as a tiny ball. Its summit is seized with two iris forceps, one on each side. A slight horizontal pull then tears the iris into two fragments. They are merely separated from each other without any upward pulling which might raise the level of the pupil.

(*d*) *Conjunctival Suture* (Fig. 6).—Immediately after the iris flaps are dropped, the conjunctiva is gently put in place and the fixation forceps is removed. Thus iris tissue has been exposed only for a few seconds. As the assistant raises the tension suture originally placed in the conjunctiva, it is an easy matter for the surgeon to place initial sutures of plain catgut on either side. Closure of the conjunctival wound is completed with additional sutures laterally.

Penicillin solution is instilled and a uniocular dressing is applied.



FIGS. 1 to 6.



FIGS. A to D.

Post-operative care

The dressing is removed after 48 hours but is always replaced at night for an additional 5 days.

Atropine is instilled twice daily for 2 days as soon as the anterior chamber is formed, usually within 2 or 3 days. Pénicillin solution is also instilled three times a day. It is noteworthy that it is exceptional for even slight posterior synechiae to develop, a substantial advantage over the Elliot trephining which is frequently complicated by an iritis.

Gonioscopic study

Gonioscopy on operated eyes is instructive in that it demonstrates anatomical details of healing, evaluation of operative technique, and affords information as to the mechanism of action of iridencleisis. François, in his paper on gonioscopy, made special mention of findings in cases operated on by our method ([12]).

Our gonioscopic observations were carried out according to Goldmann's technique with the Haag-Streit slit-lamp and a contact lens fitted with a mirror. For the sake of clarity the figures we show below are schematic.

The most frequent gonioscopic picture seen is shown in Fig. A. To the right and left, the anterior face of the iris is visible. Displacement of its fibre pattern shows that it is drawn upward, the iris is also drawn forward because the wound is anterior to Schlemm's canal. Such warping of the plane of the iris indicates that the incision was properly placed. Its absence indicates that the incision was placed too far back. The prolapsed iris outside the globe is not visible.

In the centre some of the posterior surface of the iris can be seen. It has a characteristic deeply pigmented velvety appearance even in subjects with a lightly coloured anterior surface. The angle of the anterior chamber above cannot be seen because of the position of the iris pillars. Lower down, the ciliary processes, zonule, and lens can be seen clearly.

Fig. B. shows a picture frequently seen but slightly different from that in the previous figure. Here, in the course of operation, lateral tension was sufficient to rupture the radial fibres of the iris almost to the root. A small area of grey discoloured atrophic tissue lies at the base of the tear and is nearly always easily seen. At this point where iris tissue is attached to the limbal wound, it forms two pillars which are the lateral sides of a triangle with its apex at the root of the iris.

The picture demonstrated in Fig. C. is less frequently seen. The tear in the iris is more complete, going beyond the root to form a very slight iridodialysis, consequently the iris pillars are more widely separated.

In Fig. D. it is evident that excessive tension on the iris pillars during operation caused an iridodialysis along the whole base of the coloboma. This is the exceptional finding.

REFERENCES

1. WEEKERS, L and HUBIN, R.—*Arch. d'Ophtal.*, Vol. XLVIII, p. 186, 1931.
2. WEEKERS, L.—*Arch. d'Ophtal.*, Vol. XLVIII, p. 593, 1931.
3. ——— *Arch. d'Ophtal.*, Vol. LIII, p. 166, 1936.
4. WEEKERS, L. and FANCHAMPS, J.—*Arch. d'Ophtal.*, Vol. I, p. 585, 1937.
5. WEEKERS, L.—*Bull. Soc. Ophtal , Paris.* Nancy, 16 juin, séance consacrée au traitement médical du glaucome. 1939.
6. WEEKERS, L. and BONHOMME, F.—*Ophthalmologica*, Vol. XCIX, p. 180, 1940.
7. WEEKERS, L.—*Bull. Soc. belge d'Ophtal.*, février, 1948.
8. WEEKERS, R. and HEINTZ, A.—*Bull. Soc. belge d'Ophtal.*, février, 1948.
9. WEEKERS, R. and GERARD, R.—*Bull. Soc. belge d'Ophtal.*, février, 1948.
10. WEEKERS, R. and MATHIEU, P.—*Bull. Soc. belge d'Ophtal.*, février, 1948.
11. ROUSSEL, F.—*Bull. Soc. belge d'Ophtal.*, février, 1948.
12. FRANÇOIS, J.—*Bull. Soc. belge d'Ophtal.*, février, 1948.

CARBONIC ANHYDRASE AND CATARACTA LENTIS*

BY

A. BAKKER

GRONINGEN

PROBLEMS concerning the genesis of cataract have engaged the attention of innumerable investigators throughout centuries. Measures, taken against the sequels of cataract are as old as mankind and in our days have reached a high degree of perfection. Preventive measures, however, had only success under special, limited circumstances. Cases in which we succeed in protecting individuals who may be considered as to be predestined to acquire cataracts are not very numerous, but in spite of the limited possibilities, benefits are great. Some examples may elucidate this. By the use of adequate goggles we are able to protect people against the injurious effect of radiant energy. When diseases of the thyroid gland make operation necessary, we can prevent lens opacities by taking precautions not to injure the parathyroid glands. When, however, it is not possible to avoid injury to these glands, develop-

* Received for publication, February 4, 1948.

ment of cataract can be prevented by administering irradiated ergosterol.

As prevention of course is always better than cure, we must always endeavour to get to know more and more about the causes of cataract and this means that it is necessary to have a profound knowledge of the normal functions of the lens. Now it is just this chapter of physiology which is rather inadequate, in spite of the fact that a lot of details are known about lens-metabolism (see for instance Bellows' excellent text-book which gives an exhaustive report of these questions).

As it is not yet possible to build up a logical, comprehensive entity of all the known facts, we must be content for the present to gather new material. We may suppose that all causes of cataract depend on interferences with the normal metabolic processes in the epithelium cells of the lens. The lens, suspended in a nutrient medium (aqueous humour), not supplied with blood vessels and nerves, can only maintain its transparency when all the equilibrium mechanisms go on normally. For these physiological activities the permeability of the lens capsule is of considerable importance. It is just the exceptional position of the lens which make it possible to imitate normal conditions in experiments with surviving lenses. The only difficulty is to gather nutrient fluids of adequate composition in sufficient quantities. It may be that this was the cause of the failure of many former investigators. In 1937 my attempts to find a solution for these difficulties were at last rewarded with favourable results. It could namely be established that a Ringer's solution, containing 1 per cent. glucose, injected into a rabbit's abdominal cavity, underwent so many changes in its composition within the short space of two hours, that it resembled aqueous humour very closely. With the aid of this fluid and a special culture technique, known as de Haan's perfusing culture method, I succeeded in keeping lenses alive for several weeks. R. Weekers continued my experiments and obtained many good results in studying metabolic processes of the surviving lens.

This culture method enabled me to point out some characteristics of the enzyme carbonic anhydrase. It is most probable that this enzyme plays an important part in lens metabolism. The lens contains a high concentration of it, sometimes, higher than the blood. As the aqueous humour does not contain a trace of this enzyme, it is almost certain that the lens produces its own carbonic anhydrase. The capsule is probably impermeable to it. In the explanted lenses at least, its concentration does not diminish. When sometimes the lenses in the culture vessel became opaque (a common cause was an infection of the nutrient fluid), the enzyme content decreased.

A normal rabbit's lens has an enzyme concentration of about 5 units; a lens with opacities for instance only 2 units and in cases of mature cataracts no trace of carbonic anhydrase was ever detectable. This was an invariable fact: the more the cataractous changes were pronounced, the lower the enzyme concentration was. I examined cataracts in albino rats, experimentally caused by galactose, naphthalin cataracts in rabbits, and spontaneous total cataracts in rats, dogs, rabbits, guinea-pigs, hens and a pigeon.

The human lens proved to be no exception. Two normal lenses of children had a high enzyme concentration (about the same as rabbits). It is not impossible that the true concentration was still higher, as unfortunately the measurements could not be carried out immediately after the extraction.

In two tetany patients with immature cataracts the carbonic anhydrase content was decreased to two units. In scores of mature cataracts, obtained by intra-capsular extraction, no trace of the enzyme was detectable.

Conclusion

A parallelism in the sense of decreased carbonic anhydrase activity coinciding with a lowered transparency of the lens does not absolutely prove that an inhibition of this enzyme is the only essential cause of cataract. On the contrary. All the complicated reactions which are normally and continually going on in the lens, make it probable that a disturbance of even one link of the chain of reactions will coincide with the development of lens opacities. That, however, the catalyzation by carbonic anhydrase is of great importance is undeniable. A striking example to illustrate this opinion is the fact that a drug which inhibits the function of the enzyme (*e.g.*, sulfanilamide), causes cataract.

REFERENCES

BAKKER, A.—The behaviour of a rabbit's lens and iris in a perfused culture. *Acta Neerl. Morphol.*, Vol. I, p. 97, 1937.

——— Ueber Kohlensäureanhydrase in normalen und kataraktösen Linsen. *Graefes Arch. f. Ophthal.*, Vol. CXL, p. 543, 1939.

——— Der Kohlensäureanhydrasegehalt verschiedener Augengewebe einiger Säugetiere. *Ophthalmologica*, Vol. CII, p. 351, 1941.

——— Eine Methode, die Linsen erwachsener Kaninchen auszerhalb des Körpers am Leben zu erhalten. *Graefes Arch. f. Ophthal.*, Vol. CXXXV, p. 581, 1936.

BELLOWS, J. G.—Cataract and anomalies of the lens. St. Louis, 1944.

WEEKERS, R.—Métabolisme hydrocarboné du cristallin. *Ophthalmologica*, Vol. XCVIII, p. 142, 1939.

ON THE MEASURE OF THE STEREOSCOPIC ACUITY OF VISION *

BY

J. W. NORDENSON

STOCKHOLM

SINCE the beginning of this century the International Congresses of Ophthalmology have occupied themselves with the question of internationalising certain measures and procedures of examination in our science. This work lead to the adoption of international rules and standards for the determination of the visual acuity and for the notation of the meridians in astigmatism at the XIth International Congress (Naples 1909). The work was interrupted by the first World war, but was taken up again by the XIIIth International Congress (Amsterdam 1929), at which were discussed the visual requirements for traffic and their determination. No resolution, however, was passed, but presumably these questions will now be taken up again.

Among the measures that were taken up at the XIIIth Congress for Internationalisation was also that of the acuity of stereoscopic vision. A report on that subject by Onfray was presented by the committee, in which after a review of the methods in use it was proposed that the acuity of stereoscopic vision should be determined by special stereograms giving the visual angle necessary for their being seen stereoscopically. The acuity of stereoscopic vision for the examined person would thus be given by an angle, *e.g.*, 30″, and a certain angle would be fixed for different occupations.

This way of determining the stereoscopic visual acuity is, however, open to the objection that two persons in whom the same angle of stereoscopic distinction has been found, nevertheless may have a different power of stereoscopic vision, this power depending not only of the stereoscopic angle of distinction, but also of the stereoscopic base, that is of the pupillary distance of the examined person, which varies individually.

In such circumstances it seems appropriate to choose a more exact measure for the power of stereoscopic vision, and such a measure would be the stereoscopic radius of the examined person, that is the radius of the field within which stereoscopic vision is possible. This radius, r, is the quotient of the pupillary distance, b, and the stereoscopic angle of distinction w, *i.e.*, $r = b/w$. Thus an angle of stereoscopic distinction of 3′ 0″ and a pupillary distance of 66 mm. would give a stereoscopic radius of 440 mm. and

* Received for publication, April 12, 1948.

the same angle with a pupillary distance of 54 mm. a stereoscopic radius of 360 mm.

This way of measuring the power of stereoscopic vision would not only have the advantage of paying due influence to the pupillary distance, but seems also to give a more expressive and tangible evaluation of the same. It seems therefore desirable that an exchange of the angle of distinction against the radius should be considered in the future discussion of the internationalisation of this measure.

A CASE OF SPONTANEOUS EXOPHTHALMOS DURING DELIVERY*

BY

J. GOLDBERG

EDINBURGH

A CASE of unilateral exophthalmos occurring during delivery was seen by me, and because reference to this condition in the literature is scarce, I think it of sufficient interest to put on record.

The patient, a 32 years old woman, had previously been healthy. Her blood pressure was 120/80, urine normal, Wassermann reaction of blood—negative. This was her first pregnancy and it was uneventful up to the time of delivery. Three weeks before the expected time, she started to bleed, and was sent to the hospital for induction of labour. During one of her severe pains of the second stage of labour, she suddenly complained of dimness of vision of the left eye, and protrusion of the eye was noticed. I was asked to see this patient shortly after delivery, and found the right eye completely normal. The left eye was considerably proptosed, the upper lid oedematous and the lower lid tucked away behind the proptosed eye. The cornea and conjunctiva were normal, the pupil widely and irregularly dilated without direct reaction to light and the eyeball was completely fixed. The fundus showed gross retinal oedema but details were not discernable. The eye was blind.

Two days later there was some return of movement, the upper lid showed suffusion, but no subconjunctival haemorrhages were present. The fundus was now covered with haemorrhages particularly in the macular region and the disc was pale. During the next ten days the eye movement improved in all directions except upward, the proptosis receded and the retinal haemorrhages

* Received for publication, July 16, 1948.

partially disappeared. There was some brownish discolouration of the subconjunctival tissues at the upper part of the sclera. Suddenly the proptosis increased again, the upper lid became more swollen and local pain indicated a beginning of inflammatory reaction. No elevated temperature. This subsided with penicillin and sulphadiazine. When I saw her last (about three months after the first examination) there was no exophthalmos, but optic atrophy and pigmentary and degenerative changes in the macula. The eye was blind. The explanation seems to me, a spontaneous orbital haemorrhage which produced an arterial occlusion and venous thrombosis.

I wish to thank Dr. Traquair for the help he has given me in reporting this case.

REFERENCE

BÖHM.—Ein Fall von spontaneur Exophthalmus wahrand der Geburt. *Die ophthal. Klinik III.* S. 3-5, 1899.

ANNOTATION

Medical False Quantities

At first sight our title might seem to indicate errors on the dispensing of medicines, but we may as well confess that our reflections this month are devoted to the false pronunciation of classical words. It is a matter on which the writer can speak with some authority, for if there is a chance of making a false quantity he can be relied upon to make it nine times out of ten.

To be candid, he resembles Macaulay's friend who never knew the difference between an aphorism and an apophthegm, and could be relied upon to make a dozen false quantities in as many lines of print.

Medical terms offer almost unlimited scope for the habit. Perhaps the one most usually made by every one is the shin bone. Even doctors who are classical scholars talk about a fractured tibia. But if you turn to the VIIIth Eclogue of Virgil you find that the word is a dactyl and that the first "i" is long. Angina, with the "i" long, is another false quantity that has come into common parlance. In classical verse it is "angina" with a short "i". The late Mr. Herbert Fisher once told the writer of an occasion on which he harrowed the soul of a famous schoolmaster by making a false quantity in speaking of the pituitary gland. Had he done this as a schoolboy the results might have been even more distressing than they were. After all, what does it matter? In dealing with

sick people a good clinical sense will be found of greater value than a knowledge of quantities, true or false. Many years ago a great classical scholar, a physician, was contemptuously spoken of as not knowing inflammation when he saw it. His knowledge of Homer and other classical authors had not helped him to appreciate inflammation. We confess that we have a good deal of sympathy with Thomas Holbrook, the yeoman farmer in "Cranford" who talked about Lord Birron for Byron and pronounced the name of Goethe by sounding every vowel. And had we by any chance been asked to account for Dante's name of Alighieri at school we should certainly have given Miss Wirt's notion in the Book of Snobs, that he must have come from Algiers!

FACULTY OF OPHTHALMOLOGISTS

THE following is the Honorary Secretary's summary of the business conducted at the last Council meeting held on October 8.

When it was discovered that extremely high figures were being claimed in fees for the examination of school children, the Ministry, after communication with the Honorary Secretary of the Faculty and the British Medical Association, issued a circular explaining the situation and postponing all payments until a figure had been agreed. At a meeting of the Ophthalmic Sub-Committee of the Negotiating Committee with the Ministry of Health it was agreed that the school medical service should come under the hospital service by March 31, 1949, and that in the meantime a fee of 6 guineas per session should be paid, subject to Treasury approval.

In spite of the strong recommendations of the delegates at this meeting, the Minister remained adamant that glasses prescribed privately should not be obtained free within the Service.

It has been agreed that opticians working under the Supplementary Ophthalmic Service should refer to ophthalmic surgeons all cases which did not achieve a visual acuity of 6/6.

The Ministry has suggested that hospitals should negotiate with dispensing opticians over the basis for employment. The Faculty's representatives at the meeting with the Ministry urged that this should be on a sessional and not a capitation basis.

It was learnt that the Ministry was negotiating with the ophthalmic opticians over the details of employment in hospitals and that ophthalmologists would be informed when the negotiation were complete.

The Ministry of Health has asked for nominations to a Committee to consider the question of the registration of opticians. These are

being sent forward with the collaboration of the Royal College of Surgeons of England and the British Medical Association.

As a result of representation from the Faculty, the Ministry of Labour and National Service has decided to increase the fee payable to ophthalmic medical practitioners in respect of cases referred to them by Chairmen of National Service Medical Boards from 15s. to £1 1Is. 6d. from July 5, 1948, inclusive.

The Faculty have submitted to the Examining Board in England a memorandum on Diplomas in Ophthalmology suggesting considerable modifications in the present arrangements.

Mr. F. A. Juler and Mr. Frank W. Law have been appointed to exercise a watching brief on behalf of the Faculty on the teaching and examinations conducted under the auspices of the Orthoptic Board.

The Royal College of Surgeons of England has agreed to support the Faculty's representations to the Negotiating Committee regarding the remuneration for teaching. The President of the Faculty will raise the question with the University Grants Committee.

As regards the statement which it was decided to issue in the autumn on the present political state of ophthalmological matters, it was learnt that the British Medical Association had already circularised all ophthalmologists on the Central List regarding ophthalmic matters and the Council of the Faculty decided that this would meet the case.

It has been arranged for four visitors from abroad to give lectures at the Royal College of Surgeons just before the next Congress of the Ophthalmological Society of the United Kingdom.

BOOK NOTICES

Vision and the Eye. By M. H. PIRENNE. Pp. 187. Ninety-nine figs. The Pilot Press, London. 1948.

This volume forms one of the "Frontiers of Science" series, a series of books written for the non-specialist interested in scientific subjects. To attempt to write a book of any real value to the layman on a subject so rich in phenomena as vision and covering so vast a field is a difficult task, but in it Pirenne has succeeded to a remarkable degree largely by considering a few questions in detail instead of covering the entire field in a rapid and very superficial manner: not only is the book simple and interesting but it will be of value to many specialists—and ophthalmologists. In general terms, after a concise account of the structure of the visual apparatus,

some properties of the rods and cones are discussed, spectral sensitivity curves, the energy necessary to excite vision and the nervous events it produces are described as well as the phenomena of colour vision and the linkage of the eyes with the brain. In addition to the eyes of man the properties of the eyes of insects receive notice. As would be expected, the author's own interests in the way in which the quantum nature of light enters into the phenomena of vision form one of the most interesting sections. The processes of vision are regarded as the working of a material system obeying the laws of physics; the psychological aspects of the subjects are barely touched.

Das Haftglas als optisches Instrument. By E. BÜRKI (Basle), with a foreword by Prof. A. Brückner. 322 pages. 80 figs. Bibliography. S. Karger, Basle. Price, 55 Swiss francs.

This is the most comprehensive and authoritative treatise on contact glasses which has yet appeared in the literature, embracing all aspects of our knowledge of their optics and clinical applications. The first section deals with general optics in so far as its theory is implicated in the optical system formed by the contact lens and the eye; this system in its turn is described in great detail as well as the relation of afocal lenses to axial, index and curvature ametropia and astigmatism and the optical principles of focal lenses. The value (and limitations) of such lenses in anisometropia, particularly in aphakia, their employment, particularly in a telescopic lens system in conditions wherein the visual acuity is poor, as well as their relation to the optical system in accommodation are all fully discussed. The remainder of the book is largely occupied with the practical uses of contact lenses. The history of their development is well told and the various types of lenses used from time to time from the earliest blown varieties employed during the last century to the latest types described by Dallos in England and Feinbloom in America. A detailed note is given of the many variations met with in the various countries in which such lenses are now made, whether of glass or plastic, and the problems raised in their haptics and optics are fully discussed. Finally the numerous clinical conditions wherein contact lenses are of optical or therapeutic value are detailed.

The greater part of the book is theoretical in nature and mathematical in its general formulation: to those who are not at home with mathematical optics it will not be easy to read, but there is no other comparable source where this information can be so readily obtained. The bibliography is also very comprehensive and of great value. As a general guide to the theoretical value—and limitations—of contact lenses the book stands in a class by itself.

Children's Eye Nursing. By JAMES HAMILTON DOGGART. Pp. 135. Figs. 93. London: Henry Kimpton. 1948.

This little book sets out in a precise and condensed manner all the essentials of eye nursing, which apply not only to children as the title suggests but to adults. There are 12 chapters which are concerned with the anatomy of the orbit and its contents, the causes of ocular abnormality, methods of examination, common inflammatory conditions of the eye recognised by external examination, refractive errors, strabismus, injuries, ocular therapeutics, instruments and dressings, a brief description of the main surgical principles in the commoner minor and major operations of the eye and a chapter on the care of school children.

This work is lucidly written and is profusely illustrated (93 illustrations) including 4 coloured plates of external diseases of the eye and 2 fundus paintings.

The inclusion of a picture of an ophthalmic lamp on an angle-poise bracket might be useful in the next edition for many nurses in schools and factories may have to do ophthalmic work single handed with no one to hold a lamp.

This is a useful book for any nurse, ophthalmic or general, to possess and the author is to be congratulated on his presentation of this subject.

The printing and reproduction are admirable.

CORRESPONDENCE

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—In connection with Mr. Stallard's note on the use of rubber gloves, in the October issue; the answer to Dr. Simpson's query "What is there in eye surgery that renders it immune from the laws of asepsis?" is simple: "Nothing; but the laws of asepsis are not solely, or even mainly, concerned with rubber gloves."

I have yet to meet with serious intra-ocular—or, for that matter extra-ocular infection following squint or retinal detachment operations; and, if it did occur, there are many possible causes other than the omission of gloves. The extremely slight risk of infection attributable to not using gloves must be balanced against the disadvantages of their use. People have, to my knowledge, been run over in Harley Street; yet I also know that Mr. Stallard ignores this hazard daily.

Finally, the use of the (presumably) editorial "We" and of the description "Assistant Editor" is disquieting. One can only

assume that it is intended to add weight to the opinions expressed in the Note—and this, as far as I know, represents an important departure from previous Journal policy. Does it mean "The B.J.O. says so?" If it does not, this last sentence should read "I am grateful to Dr. Simpson for his candid comments, which I personally consider correct."

Yours faithfully,

FRANK W. LAW.

36, DEVONSHIRE PLACE, W.1
October 10, 1948.

[We (editorial) are grateful to most of our correspondents, including Mr. Frank Law, for their "candid comments" and I thank him for his correction. Whatever may be the views of the Editorial Committee about the use of rubber gloves in eye surgery I will take personal responsibility for the opinion expressed in the last sentence of the note which I was instructed to write about Dr. Simpson's letter].—H. B. STALLARD, *Assistant Editor.*

NOTES

Lectures at the Royal College of Surgeons by Foreign Ophthalmologists, 1949

March 29, 5 p.m.—Professor A. Franceschetti. Cataract associated with lesions of the skin.

March 29, 6.15 p.m.—Professor G. B. Bietti. Protein and amnio-acid deficiencies in ophthalmology.

March 30, 5 p.m.—Dr. E. Hartmann. Psychosomatic symptoms in ophthalmology.

March 30, 6.15 p.m.—Professor H. J. E. Weve. Subject later.